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=> file medline caplus biosis embo biotechno uspatful
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FILE 'USPATFULL' ENTERED AT 11:13:09 ON 17 FEB 2005
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CHEMICAL SOCIETY (ACS)

=> s lr3 or lr3a or lrp5 or lrp7 or (ldl (w) receptor-related
(w) protein (w) 5)
5 FILES SEARCHED...
L1 980 LR3 OR LR3A OR LRP5 OR LRP7 OR
(LDL (W) RECEPTOR-RELATED (W)
PROTEIN (W) 5)

=> s endothelial (w) cells or osteoblasts
L2 308766 ENDOTHELIAL (W) CELLS OR
OSTEOBLASTS

=> s wnt (w) protein or dkk (w) protein
4 FILES SEARCHED...
L3 4961 WNT (W) PROTEIN OR DKK (W)
PROTEIN

=> s l1 and l2
L4 74 L1 AND L2

=> duplicate remove l4
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS,
BIOSIS, EMBASE, BIOTECHNO, USPATFULL'
KEEP DUPLICATES FROM MORE THAN ONE FILE?
Y/(N):n
PROCESSING COMPLETED FOR L4
L5 45 DUPLICATE REMOVE L4 (29
DUPLICATES REMOVED)

=> d l5 1-ibib,abs
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In a multifile environment, a format can only be used if it
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in at least one of the files. Refer to file specific help
messages
or the STNGUIDE file for information on formats
available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES
(FILEDEFAULT):ibib, abs

L5 ANSWER 1 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2005:36968 USPATFULL
TITLE: Microorganisms for therapy
INVENTOR(S): Szalay, Aladar A., Highland, CA,
UNITED STATES
Timiryasova, Tatyana, San Diego, CA,
UNITED STATES
Yu, Yong A., San Diego, CA, UNITED
STATES
Zhang, Qian, San Diego, CA, UNITED
STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005031643	A1	20050210
APPLICATION INFO.:	US 2004-872156	A1	20040618 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2003-13826	20030618
	EP 2003-18478	20030814
	EP 2003-24283	20031022
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	FISH & RICHARDSON, PC, 12390 EL CAMINO REAL, SAN DIEGO, CA, 92130-2081	
NUMBER OF CLAIMS:	86	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Page(s)	
LINE COUNT:	11773	
AB	Therapeutic methods and microorganisms therefore are provided. The microorganisms are designed to accumulate in immunoprivileged tissues and cells, such as in tumors and other proliferating tissue and in inflamed tissues, compared to other tissues, cells and organs, so that they exhibit relatively low toxicity to host organisms. The microorganisms also are designed or modified to result in leaky cell membranes of cells in which they accumulate, resulting in production of	

antibodies reactive against proteins and other cellular products and also permitting exploitation of proliferating tissues, particularly tumors, to produce selected proteins and other products. Methods for making tumor specific antibodies and also methods of making gene products encoded by the microorganism as well as antibodies reactive therewith are provided.

=> d l5 1- ibib,abs
YOU HAVE REQUESTED DATA FROM 45 ANSWERS
- CONTINUE? Y(N):y

L5 ANSWER 1 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2005:36968 USPATFULL
TITLE: Microorganisms for therapy
INVENTOR(S): Szalay, Aladar A., Highland, CA,
UNITED STATES
Timiryasova, Tatyana, San Diego, CA,
UNITED STATES
Yu, Yong A., San Diego, CA, UNITED
STATES
Zhang, Qian, San Diego, CA, UNITED
STATES

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2005031643	A1
20050210		
APPLICATION INFO.:	US 2004-872156	A1
20040618 (10)		

NUMBER	DATE
--------	------

PRIORITY INFORMATION:	EP 2003-13826
20030618	

EP 2003-18478	20030814
EP 2003-24283	20031022

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON,
PC, 12390 EL CAMINO REAL, SAN DIEGO,
CA, 92130-2081
NUMBER OF CLAIMS: 86
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 11773
AB Therapeutic methods and microorganisms
therefore are provided. The
microorganisms are designed to accumulate in
immunoprivileged tissues
and cells, such as in tumors and other proliferating
tissue and in
inflamed tissues, compared to other tissues, cells
and organs, so that
they exhibit relatively low toxicity to host
organisms. The
microorganisms also are designed or modified to
result in leaky cell
membranes of cells in which they accumulate,
resulting in production of
antibodies reactive against proteins and other
cellular products and
also permitting exploitation of proliferating tissues,
particularly

tumors, to produce selected proteins and other products. Methods for making tumor specific antibodies and also methods of making gene products encoded by the microorganism as well as antibodies reactive therewith are provided.

L5 ANSWER 2 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:320589
USPATFULL
TITLE: Rationally designed antibodies
INVENTOR(S): Bowdish, Katherine S., Del Mar,
CA, UNITED STATES
Frederickson, Shana, Solana Beach,
CA, UNITED STATES
Renshaw, Mark, Solana Beach, CA,
UNITED STATES
Orencia, Cecelia, Del Mar, CA, UNITED
STATES

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2004253242	A1
20041216		
APPLICATION INFO.:	US 2003-737290	A1
20031215 (10)		
RELATED APPLN. INFO.:	Continuation-in-part of Ser.	
No. US 2003-452590, filed		
on 2 Jun 2003, PENDING Continuation-		
in-part of Ser. No.		
US 2002-307724, filed on 2 Dec 2002,		
PENDING		
Continuation-in-part of Ser. No. US		
2001-6593, filed on		
5 Dec 2001, PENDING		

NUMBER	DATE
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PRIORITY INFORMATION:	US 2000-251448P
20001205 (60)	

US 2001-288889P	20010504 (60)
US 2001-294068P	20010529 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Mark Farber, C/O,
Alexion Pharmaceuticals, Inc., 352
Knotter Drive, Cheshire, CT, 06410
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 59 Drawing Page(s)
LINE COUNT: 5086
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Antibodies or fragments thereof having CDR
regions replaced or fused
with biologically active peptides are described.
Flanking sequences may
optionally be attached at one or both the carboxy-
terminal and
amino-terminal ends of the peptide in covalent
association with adjacent
framework regions. Compositions containing such
antibodies or fragments
thereof are useful in therapeutic and diagnostic
modalities.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 45 USPATFULL on STN

ACCESSION NUMBER: 2004:309387
USPATFULL
TITLE: Transgenic animal model of bone
mass modulation
INVENTOR(S): Askew, G. Roger, Boxford, MA,
UNITED STATES
Babij, Philip, Dunstable, MA, UNITED
STATES
Bex, Frederick James, III, Newtown
Square, PA, UNITED
STATES
Nest Bodine, Peter Van, Havertown, PA,
UNITED STATES
PATENT ASSIGNEE(S): Wyeth, Madison, NJ,
UNITED STATES, 07940 (U.S.
corporation)

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2004244069	A1
20041202		
APPLICATION INFO.:	US 2003-680287	A1
20031008 (10)		
RELATED APPLN. INFO.:	Continuation-in-part of Ser.	
No. WO 2002-US14876, filed		
on 13 May 2002, PENDING		

NUMBER	DATE
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PRIORITY INFORMATION:	US 2001-290071P	
20010511 (60)		
	US 2001-291311P	20010517 (60)
	US 2002-353058P	20020201 (60)
	US 2002-361293P	20020304 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BURNS DOANE	
SWECKER & MATHIS L L P, POST OFFICE BOX		
1404, ALEXANDRIA, VA, 22313-1404		
NUMBER OF CLAIMS:	44	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	61 Drawing Page(s)	
LINE COUNT:	8213	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB The present invention relates to methods and		
materials used to express		
the HBM protein in animal cells and transgenic		
animals. The present		
invention also relates to transgenic animals		
expressing the high bone		
mass gene, the corresponding wild-type gene, and		
mutants thereof. The		
invention provides nucleic acids, including coding		
sequences,		
oligonucleotide primers and probes, proteins,		
cloning vectors,		
expression vectors, transformed hosts, methods of		
developing		
pharmaceutical compositions, methods of		
identifying molecules involved		
in bone development, and methods of diagnosing		
and treating diseases		
involved in bone development. In preferred		
embodiments, the present		
invention is directed to methods for treating,		
diagnosing and preventing		
osteoporosis.		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:299859
USPATFULL
TITLE: Compositions and methods for
treating osteoporosis
INVENTOR(S): Stoch, Selwyn Aubrey, Clark,
NJ, UNITED STATES
Orloff, John, Princeton Junction, NJ,
UNITED STATES

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2004235728	A1
20041125		
APPLICATION INFO.:	US 2004-494542	A1
20040430 (10)		
WO 2002-US35341		20021104

NUMBER	DATE
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PRIORITY INFORMATION:	US 2001-337785P
20011108 (60)	
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MERCK AND CO INC, P
O BOX 2000, RAHWAY, NJ, 070650907	
NUMBER OF CLAIMS:	19
EXEMPLARY CLAIM:	1
LINE COUNT:	1427
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The present invention relates to pharmaceutical	
compositions comprising	
a cathepsin K inhibitor which are useful for treating	
such conditions as	
bone resorption, osteoporosis, arthritis, tumor	
metastases, Paget's	
disease, and other metabolic bone disorders	
characterized by increased	
bone resorption.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:282022
USPATFULL
TITLE: Transgenic animal model of bone
mass modulation
INVENTOR(S): Babij, Philip, Newbury Park, CA,
UNITED STATES
Bex, Frederick James, Newton Square,
PA, UNITED STATES
Bodine, Peter Van Nest, Havertown, PA,
UNITED STATES
Askew, G. Roger, Boxford, MA, UNITED
STATES

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2004221326	A1
20041104		
APPLICATION INFO.:	US 2004-477238	A1
20040412 (10)		
WO 2002-US14876		20020513

NUMBER	DATE
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PRIORITY INFORMATION:	US 2001-60290071
20010511	
	US 2001-60291311
	20010517
	US 2002-60353058
	20020201

US 2002-60361293 20020304
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BURNS DOANE
SWECKER & MATHIS L L P, POST OFFICE BOX
1404, ALEXANDRIA, VA, 22313-1404
NUMBER OF CLAIMS: 58
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 61 Drawing Page(s)
LINE COUNT: 7878
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and materials used to express
the HBM protein in animal cells and transgenic animals. The present
invention also relates to transgenic animals expressing the high bone
mass gene, the corresponding wild-type gene, and mutants thereof. The
invention provides nucleic acids, including coding sequences,
oligonucleotide primers and probes, proteins, cloning vectors,
expression vectors, transformed hosts, methods of developing
pharmaceutical compositions, methods of identifying molecules involved
in bone development, and methods of diagnosing and treating diseases
involved in bone development. In preferred embodiments, the present
invention is directed to methods for treating, diagnosing and preventing
osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:275671
USPATFULL
TITLE: Compositions and methods for characterizing and
regulating Wnt pathways
INVENTOR(S): MacDougald, Ormond A.,
Ypsilanti, MI, UNITED STATES
Longo, Kenneth A., Ann Arbor, MI,
UNITED STATES
Ross, Sarah E., Cambridge, MA,
UNITED STATES
PATENT ASSIGNEE(S): The Regents of the
University of Michigan, Ann Arbor,
MI (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004216176	A1
20041028		
APPLICATION INFO.:	US 2004-755594	A1
20040112	(10)	

NUMBER	DATE
PRIORITY INFORMATION:	US 2003-439386P
20030110	(60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Tanya A. Arenson, MEDLEN & CARROLL, LLP, Suite 350, 101 Howard Street, San Francisco, CA,
94105	

NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 1162
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to transgenic animal models for altered
Wnt expression. The present invention also provides methods for
generating animal models and screening methods for identifying
biologically active compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:228196
USPATFULL
TITLE: High bone mass gene of 11q13.3
INVENTOR(S): Carulli, John P., Southboro, MA,
UNITED STATES
Little, Randall D., Newtonville, MA,
UNITED STATES
Recker, Robert R., Omaha, NE, UNITED
STATES
Johnson, Mark L., Omaha, NE, UNITED
STATES
PATENT ASSIGNEE(S): Genome Therapeutics
Corporation, Waltham, MA, UNITED
STATES (U.S. corporation)
Creighton University, Omaha, NE,
UNITED STATES (U.S.
corporation)

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004176582	A1
20040909		
APPLICATION INFO.:	US 2003-731739	A1
20031210	(10)	
RELATED APPLN. INFO.:	Division of Ser. No. US	
2000-544398,	filed on 5 Apr	
	2000, PENDING Continuation-in-part of	
Ser. No. US		
	1999-229319, filed on 13 Jan 1999,	
ABANDONED		

NUMBER	DATE
PRIORITY INFORMATION:	US 1998-71449P
19980113	(60)
	US 1998-105511P 19981023 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	BURNS DOANE
SWECKER & MATHIS L L P, POST OFFICE BOX	
1404, ALEXANDRIA, VA, 22313-1404	
NUMBER OF CLAIMS:	74
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	32 Drawing Page(s)
LINE COUNT:	12994
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The present invention relates to methods and materials used to isolate and detect a high bone mass gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The	

genes identified in the present invention are implicated in bone development. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:197578
USPATFULL

TITLE: Lp mammalian proteins; related reagents
INVENTOR(S): Amegadzie, Bernard Yaovi,
Malvern, PA, UNITED STATES
Basinski, Margaret Barbara,
Indianapolis, IN, UNITED STATES
Scott, William L., Indianapolis, IN,
UNITED STATES LR
Chen, Dayue, Carmel, IN, UNITED STATES
Huang, Chongxi, Indianapolis, IN,
UNITED STATES
Keleher, Gerald Patrick, Indianapolis, IN,
UNITED STATES
Perkins, Douglas Raymond, New
Palestine, IN, UNITED STATES
Rostek, Paul Robert, Indianapolis, IN,
UNITED STATES
Rowlinson, Scott William, Indianapolis,
IN, UNITED STATES
Sankhavaram, Patanjali Raghavac,
Carmel, IN, UNITED STATES
Seno, Eugene Thomas, Weybridge, VT,
UNITED STATES
Su, Eric Wen, Carmel, IN, UNITED STATES
Zhi, Yu, Indianapolis, IN, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004152885	A1	
	20040805		
APPLICATION INFO.:	US 2003-480172	A1	
	20030827	(10)	

WO 2002-US5093 20020301
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Gerald P keleher, Eli Lilly & Company, Patent Division,
PO Box 6288, Indianapolis, IN, 46206-6288

NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 12032
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Isolated nucleic acid molecules encoding polypeptides from a human, reagents related thereto (including purified polypeptides specific antibodies) are provided. Methods of using said reagents and diagnostic kits are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 9 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:197345
USPATFULL
TITLE: Regulation of transcription elongation factors
INVENTOR(S): Rana, Tariq M., Shrewsbury, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004152651	A1	
	20040805		
APPLICATION INFO.:	US 2003-635854	A1	
	20030805	(10)	

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-423198P	
	20021101 (60)	
	US 2003-439301P	20030109 (60)
	US 2002-433097P	20021213 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LAHIVE & COCKFIELD, LLP., 28 STATE STREET, BOSTON, MA, 02109	
NUMBER OF CLAIMS:	87	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	40	Drawing Page(s)
LINE COUNT:	5412	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB	The present invention relates to agents, including siRNA and shRNA molecules, small molecules, antisense strands, and ribozymes that are targeted to transcription elongation factors (TEFs), including CDK9 and CycT1, subunits of P-TEFb, Spt4 and Spt5, subunits of DSIF (DRB Sensitivity-Inducing Factor (DSIF)), and Spt6. The present invention also relates to methods for treating disorders associated with aberrant or unwanted TEF expression or activity, including HIV and disorders characterized by unwanted or aberrant cellular proliferation or differentiation, such as cancer.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 10 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:196424
USPATFULL
TITLE: Lectin compositions and methods for modulating an

immune response to an antigen
INVENTOR(S): Segal, Andrew H., Boston, MA,
UNITED STATES
Young, Elihu, Sharon, MA, UNITED
STATES
PATENT ASSIGNEE(S): Genitrix, LLC (U.S.
corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004151728 A1 20040805		
APPLICATION INFO.: US 2003-666834 A1 20030919 (10)		
RELATED APPLN. INFO.: Division of Ser. No. US 2003-645000, filed on 20 Aug 2003, PENDING		

NUMBER	DATE
PRIORITY INFORMATION: US 2002-404823P 20020820 (60)	
US 2003-487407P 20030715 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: PALMER & DODGE, LLP, KATHLEEN M. WILLIAMS, 111 HUNTINGTON AVENUE, BOSTON, MA, 02199	
NUMBER OF CLAIMS: 77	
EXEMPLARY CLAIM: 1	
LINE COUNT: 39129	
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB The present invention provides a fusion polypeptide which can bind to a cell surface binding moiety (e.g., a carbohydrate) and serve as a ligand for a cell surface polypeptide, as well as a vector comprising a nucleic acid encoding for such a fusion polypeptide, and a host cell comprising such nucleic acid. The present invention also provides a composition comprising an antigen bearing target and such a fusion polypeptide, as well as a composition comprising a virus or a cell and such a fusion polypeptide. The present invention further relates to a method of modulating an immune response in an animal using such compositions.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 11 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:178323
USPATFULL
TITLE: Molecular determinants of myeloma
bone disease and uses
thereof
INVENTOR(S): Shaughnessy, John D., Little
Rock, AR, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004137489 A1 20040715		
APPLICATION INFO.: US 2003-727461 A1 20031204 (10)		

NUMBER	DATE
PRIORITY INFORMATION: US 2002-431040P 20021205 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: Benjamin Aaron Adler, ADLER & ASSOCIATES, 8011 Candle Lane, Houston, TX, 77071	
NUMBER OF CLAIMS: 14	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 43 Drawing Page(s)	
LINE COUNT: 1105	
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB To identify molecular determinants of lytic bone disease in multiple myeloma, the expression profiles of .about.12,000 genes in CD138-enriched plasma cells from newly diagnosed multiple myeloma patients exhibiting no radiological evidence of lytic lesions (n=28) were compared to those with .gtoreq.3 lytic lesions (n=47). Two secreted WNT signaling antagonists, soluble frizzled related protein 3 (SFRP-3/FRZB) and the human homologue of Dickkopf-1 (DKK1), were expressed in 40 of 47 with lytic bone lesions, but only 16 of 28 lacking bone lesions (P<0.05). DKK1 and FRZB were not expressed in plasma cells from 45 normal bone marrow donors or 10 Waldenstrom's macroglobulinemia, a related plasma cells malignancy that lacks bone disease. These data indicate that these factors are important mediators of multiple myeloma bone disease, and inhibitors of these proteins may be used to block bone disease.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 12 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:165307
USPATFULL
TITLE: Lectin compositions and methods for
modulating an
immune response to an antigen
INVENTOR(S): Segal, Andrew H., Boston, MA,
UNITED STATES
Young, Elihu, Sharon, MA, UNITED
STATES
PATENT ASSIGNEE(S): Genitrix, LLC (U.S.
corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004126793 A1 20040701		
APPLICATION INFO.: US 2003-666885 A1 20030919 (10)		
RELATED APPLN. INFO.: Division of Ser. No. US 2003-645000, filed on 20 Aug 2003, PENDING		

NUMBER	DATE
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PRIORITY INFORMATION: US 2002-404823P
20020820 (60)

US 2003-487407P 20030715 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PALMER & DODGE,
LLP, KATHLEEN M. WILLIAMS, 111
HUNTINGTON AVENUE, BOSTON,
MA, 02199

NUMBER OF CLAIMS: 147

EXEMPLARY CLAIM: 1

LINE COUNT: 28979

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a fusion polypeptide which can bind to a cell surface binding moiety (e.g., a carbohydrate) and serve as a ligand for a cell surface polypeptide, as well as a vector comprising a nucleic acid encoding for such a fusion polypeptide, and a host cell comprising such nucleic acid. The present invention also provides a composition comprising an antigen bearing target and such a fusion polypeptide, as well as a composition comprising a virus or a cell and such a fusion polypeptide. The present invention further relates to a method of modulating an immune response in an animal using such compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 13 OF 45 USPATFULL on STN

ACCESSION NUMBER: 2004:164872

USPATFULL

TITLE: Lectin compositions and methods for modulating an

immune response to an antigen

INVENTOR(S): Segal, Andrew H., Boston, MA,
UNITED STATES

Young, Elihu, Sharon, MA, UNITED

STATES

PATENT ASSIGNEE(S): Genitrix, LLC (U.S.
corporation)

NUMBER KIND DATE

PATENT INFORMATION: US 2004126357 A1
20040701

APPLICATION INFO.: US 2003-666886 A1
20030919 (10)

RELATED APPLN. INFO.: Division of Ser. No. US
2003-645000, filed on 20 Aug
2003, PENDING

NUMBER DATE

PRIORITY INFORMATION: US 2002-404823P
20020820 (60)

US 2003-487407P 20030715 (60)
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PALMER & DODGE,
LLP, KATHLEEN M. WILLIAMS, 111
HUNTINGTON AVENUE, BOSTON,
MA, 02199

NUMBER OF CLAIMS: 11

EXEMPLARY CLAIM: 1

LINE COUNT: 39007

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a fusion polypeptide which can bind to a cell surface binding moiety (e.g., a carbohydrate) and serve as a ligand for a cell surface polypeptide, as well as a vector comprising a nucleic acid encoding for such a fusion polypeptide, and a host cell comprising such nucleic acid. The present invention also provides a composition comprising an antigen bearing target and such a fusion polypeptide, as well as a composition comprising a virus or a cell and such a fusion polypeptide. The present invention further relates to a method of modulating an immune response in an animal using such compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 14 OF 45 USPATFULL on STN

ACCESSION NUMBER: 2004:51429 USPATFULL

TITLE: Reagents and methods for

modulating dkk-mediated

interactions

INVENTOR(S): Allen, Kristina M., Hopkinton,
MA, UNITED STATES

Anisowicz, Anthony, West Newton, MA,

UNITED STATES

Damagnez, Veronique, Framingham,

MA, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2004038860 A1
20040226

APPLICATION INFO.: US 2002-182936 A1
20020802 (10)

WO 2002-US15982 20020517

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BURNS DOANE
SWECKER & MATHIS L L P, POST OFFICE BOX
1404, ALEXANDRIA, VA, 22313-1404

NUMBER OF CLAIMS: 114

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 33 Drawing Page(s)

LINE COUNT: 5224

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides reagents, compounds, compositions, and methods relating to novel interactions of the extracellular domain of ***LRP5***, HBM (a variant of ***LRP5***), and/or LRP6 with Dkk, including Dkk-1. The various nucleic acids, polypeptides, antibodies, assay methods, diagnostic methods, and methods of treatment of the present invention are related to and impact on Dkk, ***LRP5***, LRP6, HBM, and Wnt signaling. Dkk, ***LRP5***, LRP6, HBM, and Wnt are implicated in bone and lipid cellular signaling. Thus, the present invention provides reagents and methods for modulating lipid levels

and/or bone mass and is useful in the treatment and diagnosis of abnormal lipid levels and bone mass disorders, such as osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 15 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:44501 USPATFULL
TITLE: Proteins and nucleic acids encoding same

INVENTOR(S): Tchernev, Velizar T., Branford, CT, UNITED STATES

Spytek, Kimberly A., New Haven, CT, UNITED STATES

Zerhusen, Bryan D., Branford, CT, UNITED STATES

Patturajan, Meera, Branford, CT, UNITED STATES

Shimkets, Richard A., West Haven, CT, UNITED STATES

Li, Li, Branford, CT, UNITED STATES
Gangolli, Esha A., Madison, CT, UNITED STATES

Padigaru, Muralidhara, Branford, CT, UNITED STATES

Anderson, David W., Branford, CT, UNITED STATES

Rastelli, Luca, Guilford, CT, UNITED STATES

Miller, Charles E., Hill Drive, CT, UNITED STATES

Gerlach, Valerie, Branford, CT, UNITED STATES

Taupier, Raymond J., JR., East Haven, CT, UNITED STATES

Gusev, Vladimir Y., UNITED STATES
Colman, Steven D., Guilford, CT, UNITED STATES

Wolenc, Adam Ryan, New Haven, CT, UNITED STATES

Pena, Carol E. A., Guilford, CT, UNITED STATES

Furtak, Katarzyna, Anosia, CT, UNITED STATES

Grosse, William M., Bransford, CT, UNITED STATES

Alsobrook, John P., II, Madison, CT, UNITED STATES

Lepley, Denise M., Branford, CT, UNITED STATES

Rieger, Daniel K., Branford, CT, UNITED STATES

Burgess, Catherine E., Wethersfield, CT, UNITED STATES

UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004033493	A1
20040219		
APPLICATION INFO.:	US 2002-72012	A1
20020131 (10)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2001-267459P
20010208 (60)	
US 2001-266975P	20010207 (60)
US 2001-267057P	20010207 (60)
US 2001-266767P	20010205 (60)

US 2001-266406P	20010202 (60)
US 2001-265395P	20010131 (60)
US 2001-265412P	20010131 (60)
US 2001-265517P	20010131 (60)
US 2001-265514P	20010131 (60)
US 2001-267823P	20010209 (60)
US 2001-268974P	20010215 (60)
US 2001-271855P	20010227 (60)
US 2001-271839P	20010227 (60)
US 2001-273046P	20010302 (60)
US 2001-272788P	20010302 (60)
US 2001-275989P	20010314 (60)
US 2001-275925P	20010314 (60)
US 2001-275947P	20010314 (60)
US 2001-275950P	20010314 (60)
US 2001-276450P	20010315 (60)
US 2001-276448P	20010315 (60)
US 2001-276397P	20010316 (60)
US 2001-276768P	20010316 (60)
US 2001-278652P	20010320 (60)
US 2001-278775P	20010326 (60)
US 2001-278778P	20010326 (60)
US 2001-279882P	20010329 (60)
US 2001-279884P	20010329 (60)
US 2001-280147P	20010330 (60)
US 2001-283083P	20010411 (60)
US 2001-282992P	20010411 (60)
US 2001-285133P	20010420 (60)
US 2001-285749P	20010423 (60)
US 2001-288327P	20010503 (60)
US 2001-288504P	20010503 (60)
US 2001-294047P	20010529 (60)
US 2001-294473P	20010530 (60)
US 2001-296964P	20010608 (60)
US 2001-298959P	20010618 (60)
US 2001-299324P	20010619 (60)
US 2001-312020P	20010813 (60)
US 2001-312908P	20010816 (60)
US 2001-312889P	20010816 (60)
US 2001-313930P	20010821 (60)
US 2001-315470P	20010828 (60)
US 2001-316447P	20010831 (60)
US 2001-318115P	20010907 (60)
US 2001-318118P	20010907 (60)
US 2001-318740P	20010912 (60)
US 2001-323379P	20010919 (60)
US 2001-330308P	20011018 (60)
US 2001-330245P	20011018 (60)
US 2001-332701P	20011114 (60)
US 2001-271664P	20010226 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ivor R. Elrif, Ph.D.,
Mintz, Levin, Cohn, Ferris,,
Glovsky and Popeo, P.C., One Financial
Center, Boston,
MA, 02111

NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
LINE COUNT: 59681
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of

the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 16 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:31217 USPATFULL
TITLE: Wise/Sost nucleic acid sequences
and amino acid

sequences
INVENTOR(S): Krumlauf, Robb, Mission Hills,
KS, UNITED STATES
Ellies, Debra, Kansas City, MO, UNITED
STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004023356 A1 20040205		
APPLICATION INFO.: US 2003-464368 A1 20030616 (10)		

NUMBER	DATE
PRIORITY INFORMATION: US 2002-388970P 20020614 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: POLSINELLI SHALTON & WELTE, P.C., Suite 1000, 700 W. 47th Street, Kansas City, MO, 64108	
NUMBER OF CLAIMS: 235	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 18 Drawing Page(s)	
LINE COUNT: 4672	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The present invention relates to nucleic acid sequences and amino acid sequences which influence bone deposition, the Wnt pathway, ocular development, tooth development, and may bind to LRP. The nucleic acid sequence and polypeptides include Wise and Sost as well as a family of molecules which express a cysteine knot polypeptide. Additionally, the present invention relates to various molecular tools derived from the nucleic acids and polypeptides including vectors, transfected host cells, monochronal antibodies, Fab fragments, and methods for impacting the pathways.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 17 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:18907 USPATFULL
TITLE: Compositions and methods for
modulating cell

differentiation
INVENTOR(S): Lassar, Andrew B., Newton
Center, MA, UNITED STATES
Mercola, Mark, Del Mar, CA, UNITED
STATES

Gupta, Ruchika, San Diego, CA,
UNITED STATES
Marvin, Martha, Brookline, MA, UNITED
STATES
Schneider, Valerie, Philadelphia, PA,
UNITED STATES
Tzahor, Eldad, Brookline, MA, UNITED
STATES
Brott, Barbara, Boston, MA, UNITED
STATES
Sokol, Sergei, Boston, MA, UNITED
STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004014209 A1 20040122		
APPLICATION INFO.: US 2003-351275 A1 20030123 (10)		

NUMBER	DATE
PRIORITY INFORMATION: US 2002-351126P 20020123 (60)	
US 2002-352456P 20020128 (60)	
US 2002-352665P 20020129 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: FOLEY HOAG, LLP, PATENT GROUP, WORLD TRADE CENTER WEST, 155 SEAPORT BLVD, BOSTON, MA, 02110	
NUMBER OF CLAIMS: 61	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 24 Drawing Page(s)	
LINE COUNT: 4008	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The present invention relates to compositions and methods for stimulating differentiation of stem cells into cardiac cells. The methods of the invention involve contacting a population cells comprising stem cells with at least one Wnt antagonist, such as a polypeptide or polypeptide fragment. In certain embodiments, the methods of the invention involve Dkk proteins or fragments, homologs, derivatives, variants, or peptidomimetics thereof.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 18 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:13385 USPATFULL
TITLE: Proteins and nucleic acids encoding
same
INVENTOR(S): Alsobrook, John P., II, Madison,
CT, UNITED STATES
Anderson, David W., Branford, CT,
UNITED STATES
Ballinger, Robert A., Newington, CT,
UNITED STATES
Boldog, Ference L., North Haven, CT,
UNITED STATES
Burgess, Catherine E., Wethersfield, CT,
UNITED STATES
Casman, Stacie J., North Haven, CT,
UNITED STATES

STATES Ellerman, Karen, Branford, CT, UNITED
 STATES Gangolli, Esha A., Madison, CT,
 UNITED STATES Gerlach, Valerie, Branford, CT, UNITED
 STATES Gilbert, Jennifer A., Madison, CT,
 UNITED STATES Gorman, Linda, Branford, CT, UNITED
 STATES Guo, Xiaojia (Sasha), Branford, CT,
 UNITED STATES Gusev, Vladimir Y., Madison, CT,
 UNITED STATES Kekuda, Ramesh, Norwalk, CT, UNITED
 STATES Li, Li, Branford, CT, UNITED STATES
 STATES Liu, Xiaohong, Branford, CT, UNITED
 STATES Malyankar, Uriel M., Branford, CT,
 UNITED STATES Miller, Charles E., Guilford, CT, UNITED
 STATES Millet, Isabelle, Milford, CT, UNITED
 STATES Padigar, Muralidhara, Branford, CT,
 UNITED STATES Patturajan, Meera, Branford, CT,
 UNITED STATES A. Pena, Carol E., New Haven, CT,
 UNITED STATES Peyman, John A., New Haven, CT,
 UNITED STATES Rastelli, Luca, Guilford, CT, UNITED
 STATES Shenoy, Suresh G., Branford, CT,
 UNITED STATES Shimkets, Richard A., Guilford, CT,
 UNITED STATES Smithson, Glennda, Guilford, CT,
 UNITED STATES Spytek, Kimberly A., New Haven, CT,
 UNITED STATES Stone, David J., Guilford, CT, UNITED
 STATES Taupier, Raymond J., JR., East Haven,
 CT, UNITED STATES Tchernev, Velizar T., Branford, CT,
 UNITED STATES Vernet, Corine A.M., Branford, CT,
 UNITED STATES Zerhusen, Bryan D., Branford, CT,
 UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004009907	A1
20040115		
APPLICATION INFO.:	US 2002-85198	A1
20020225 (10)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2001-271646P
20010226 (60)	
US 2001-276401P	20010316 (60)
US 2001-311981P	20010813 (60)
US 2001-312858P	20010816 (60)
US 2001-271840P	20010227 (60)
US 2001-277324P	20010320 (60)

US 2001-286096P	20010424 (60)
US 2001-299695P	20010620 (60)
US 2001-315614P	20010829 (60)
US 2001-272405P	20010228 (60)
US 2001-272410P	20010228 (60)
US 2001-272414P	20010228 (60)
US 2001-278660P	20010320 (60)
US 2001-280234P	20010330 (60)
US 2001-272404P	20010228 (60)
US 2001-280039P	20010330 (60)
US 2001-313280P	20010817 (60)
US 2001-322818P	20010917 (60)
US 2001-273300P	20010302 (60)
US 2001-280818P	20010402 (60)
US 2001-288353P	20010503 (60)
US 2001-294834P	20010531 (60)
US 2001-299845P	20010621 (60)
US 2001-272922P	20010302 (60)
US 2001-272787P	20010302 (60)
US 2001-285754P	20010423 (60)
US 2001-303242P	20010705 (60)
US 2001-273048P	20010302 (60)
US 2001-283443P	20010412 (60)
US 2001-291703P	20010517 (60)

DOCUMENT TYPE: Utility
 FILE SEGMENT: APPLICATION
 LEGAL REPRESENTATIVE: Ivor R. Elrifi, MINTZ,
 LEVIN, COHN, FERRIS, GLOVSKY
 and POPEO, P.C., One Financial
 Center, Boston, MA,
 02111
 NUMBER OF CLAIMS: 49
 EXEMPLARY CLAIM: 1
 LINE COUNT: 46330
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Disclosed herein are nucleic acid sequences that
 encode novel
 polypeptides. Also disclosed are polypeptides
 encoded by these nucleic
 acid sequences, and antibodies, which
 immunospecifically-bind to the
 polypeptide, as well as derivatives, variants,
 mutants, or fragments of
 the aforementioned polypeptide, polynucleotide, or
 antibody. The
 invention further discloses therapeutic, diagnostic
 and research methods
 for diagnosis, treatment, and prevention of
 disorders involving any one
 of these novel human nucleic acids and proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 19 OF 45 USPATFULL on STN
 ACCESSION NUMBER: 2004:13003 USPATFULL
 TITLE: Diagnosis, prognosis and
 identification of potential
 therapeutic targets of multiple myeloma
 based on gene
 expression profiling
 INVENTOR(S): Shaughnessy, John D., Little
 Rock, AR, UNITED STATES
 Zhan, Fenghuang, Little Rock, AR,
 UNITED STATES
 Barlogie, Bart, Little Rock, AR, UNITED
 STATES

NUMBER	KIND	DATE
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PATENT INFORMATION: US 2004009523 A1
20040115
APPLICATION INFO.: US 2003-454263 A1
20030604 (10)
RELATED APPLN. INFO.: Continuation-in-part of Ser.
No. US 2003-409004, filed
on 8 Apr 2003, PENDING Continuation-
in-part of Ser. No.
US 2002-289746, filed on 7 Nov 2002,
PENDING

NUMBER	DATE
PRIORITY INFORMATION: US 2002-403075P 20020813 (60)	
US 2001-348238P	20011107 (60)
US 2002-355386P	20020208 (60)
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: Benjamin Aaron Adler, ADLER & ASSOCIATES, 8011 Candle Lane, Houston, TX, 77071	
NUMBER OF CLAIMS: 26	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 24 Drawing Page(s)	
LINE COUNT: 4510	
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB Gene expression profiling between normal B cells/plasma cells and multiple myeloma cells revealed four distinct subgroups of multiple myeloma plasma cells that have significant correlation with clinical characteristics known to be associated with poor prognosis. Diagnosis for multiple myeloma (and possibly monoclonal gammopathy of undetermined significance) based on differential expression of 14 genes, as well as prognostics for the four subgroups of multiple myeloma based on the expression of 24 genes were also established. Gene expression profiling also allows placing multiple myeloma into a developmental schema parallel to that of normal plasma cell differentiation. The development of a gene expression- or developmental stage- based classification system for multiple myeloma would lead to rational design of more accurate and sensitive diagnostics, prognostics and tumor- specific therapies for multiple myeloma.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 20 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:211474
USPATFULL
TITLE: High bone mass gene of 1.1q13.3
INVENTOR(S): Carulli, John P., Southboro, MA,
United States
Little, Randall D., Newtonville, MA,
United States
Recker, Robert R., Omaha, NE, United
States
Johnson, Mark L., Omaha, NE, United
States

PATENT ASSIGNEE(S): Genome Therapeutics
Corporation, Waltham, MA, United
States (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 6780609	B1	
20040824		
APPLICATION INFO.: US 2000-543771		
20000405 (9)		
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-229319, filed on 13 Jan 1999, now abandoned		

NUMBER	DATE
PRIORITY INFORMATION: US 1998-105511P 19981023 (60)	
US 1998-71449P	19980113 (60)
DOCUMENT TYPE: Utility	
FILE SEGMENT: GRANTED	
PRIMARY EXAMINER: Fredman, Jeffrey	
ASSISTANT EXAMINER: Kaushal, Sumesh	
LEGAL REPRESENTATIVE: Burns, Doane, Swecker & Mathis, L.L.P.	
NUMBER OF CLAIMS: 8	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 36 Drawing Figure(s); 32 Drawing Page(s)	
LINE COUNT: 11922	
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB The present invention relates to methods and materials used to isolate and detect a high bone mass gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The genes identified in the present invention are implicated in bone development. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 21 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2004:192608
USPATFULL
TITLE: High bone mass gene of 11q13.3
INVENTOR(S): Carulli, John P., Southboro, MA,
United States
Little, Randall D., Newtonville, MA,
United States
Recker, Robert R., Omaha, NE, United
States

Johnson, Mark L., Omaha, NE, United States
PATENT ASSIGNEE(S): Genome Therapeutics Corporation, Waltham, MA, United States (U.S. corporation)
Creighton University School of Medicine, Omaha, NE, United States (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 6770461 B1		
20040803		
APPLICATION INFO.: US 2000-544398		
20000405 (9)		
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-229319, filed on 13 Jan 1999		

NUMBER	DATE
PRIORITY INFORMATION: US 1998-105511P	
19981023 (60)	
US 1998-71449P 19980113 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: GRANTED	
PRIMARY EXAMINER: Falk, Anne-Marie	
ASSISTANT EXAMINER: Qian, Celine	
LEGAL REPRESENTATIVE: Burns, Doane, Swecker & Mathis, L.L.P.	
NUMBER OF CLAIMS: 24	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 36 Drawing Figure(s); 32 Drawing Page(s)	
LINE COUNT: 11938	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The present invention relates to methods and materials used to isolate and detect a high bone mass gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The genes identified in the present invention are implicated in bone development. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 22 OF 45 MEDLINE on STN
DUPLICATE 1
ACCESSION NUMBER: 2004244690 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15143163
TITLE: The ***LRP5*** high-bone-mass G171V mutation disrupts

LRP5 interaction with Mesd.
AUTHOR: Zhang Yazhou; Wang Yang; Li Xiaofeng; Zhang Jianhong; Mao Junhao; Li Zhong; Zheng Jie; Li Lin; Harris Steve; Wu Dianqing
CORPORATE SOURCE: Department of Genetics and Developmental Biology, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06410, USA.
CONTRACT NUMBER: CA85420 (NCI) GM54167 (NIGMS)
SOURCE: Molecular and cellular biology, (2004 Jun) 24 (11) 4677-84.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040515
Last Updated on STN: 20040624
Entered Medline: 20040621

AB The mechanism by which the high-bone-mass (HBM) mutation (G171V) of the Wnt coreceptor ***LRP5*** regulates canonical Wnt signaling was investigated. The mutation was previously shown to reduce DKK1-mediated antagonism, suggesting that the first YWTD repeat domain where G171 is located may be responsible for DKK-mediated antagonism. However, we found that the third YWTD repeat, but not the first repeat domain, is required for DKK1-mediated antagonism. Instead, we found that the G171V mutation disrupted the interaction of ***LRP5*** with Mesd, a chaperone protein for ***LRP5*** /6 that is required for transport of the coreceptors to cell surfaces, resulting in fewer ***LRP5*** molecules on the cell surface. Although the reduction in the number of cell surface ***LRP5*** molecules led to a reduction in Wnt signaling in a paracrine paradigm, the mutation did not appear to affect the activity of coexpressed Wnt in an autocrine paradigm. Together with the observation that osteoblast cells produce autocrine canonical Wnt, Wnt7b, and that osteocytes produce paracrine DKK1, we think that the G171V mutation may cause an increase in Wnt activity in ***osteoblasts*** by reducing the number of targets for paracrine DKK1 to antagonize without affecting the activity of autocrine Wnt.

L5 ANSWER 23 OF 45 MEDLINE on STN
DUPLICATE 2
ACCESSION NUMBER: 2004212083 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15110782
TITLE: Glucocorticoid enhances the expression of dickkopf-1 in

human ***osteoblasts*** : novel mechanism of glucocorticoid-induced osteoporosis.
 AUTHOR: Ohnaka Keizo; Taniguchi Hiroshi; Kawate Hisaya; Nawata Hajime; Takayanagi Ryoichi
 CORPORATE SOURCE: Department of Geriatric Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan..
 oonaka@geriat.med.kyushu-u.ac.jp
 SOURCE: Biochemical and biophysical research communications, (2004 May 21) 318 (1) 259-64.
 Journal code: 0372516. ISSN: 0006-291X.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200406
 ENTRY DATE: Entered STN: 20040428
 Last Updated on STN: 20040609
 Entered Medline: 20040608
 AB To clarify the underlying mechanism of glucocorticoid-induced osteoporosis, we investigated the effect of glucocorticoid on the expression of dickkopf-1 (Dkk-1), an antagonist of Wnt signaling, in primary cultured human ***osteoblasts***. Dexamethasone markedly induced the expression of mRNA for Dkk-1 in a dose- and time-dependent manner. The expression of Kremen1, a receptor for Dkk, did not change by the treatment with dexamethasone, while that of low-density lipoprotein receptor-related protein 5 (***LRP5***), a Wnt coreceptor, slightly decreased by the treatment with dexamethasone. Dexamethasone increased the transcriptional activity of the Dkk-1 gene promoter in human ***osteoblasts***. Serial deletion and mutation analyses of the Dkk-1 promoter showed that one putative glucocorticoid responsive element-like sequence located from -788 to -774bp is essential for the enhancement of the Dkk-1 promoter activity by dexamethasone in human ***osteoblasts***. Since the Wnt signal is now recognized as a crucial regulator for bone formation, the Dkk-1 enhanced by glucocorticoid may inhibit the Wnt signal in ***osteoblasts***, which may be involved in the pathogenesis of glucocorticoid-induced osteoporosis.

L5 ANSWER 24 OF 45 MEDLINE on STN
 ACCESSION NUMBER: 2004199481 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15095618
 TITLE: [Wnt/ ***LRP5***, a new regulation osteoblastic pathway involved in reaching peak bone masses].
 Wnt/ ***LRP5***, une nouvelle voie de regulation

osteoblastique impliquee dans l'acquisition du pic de masses osseuses.
 AUTHOR: Caverzasio Joseph
 CORPORATE SOURCE: Service des maladies osseuses Departement de rehabilitation et geriatrie HUG..
 Joseph.Caverzasio@medecine.unige.ch
 SOURCE: Revue medicale de la Suisse romande, (2004 Feb) 124 (2) 81-2.
 Journal code: 0421524. ISSN: 0035-3655.
 PUB. COUNTRY: Switzerland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: French
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200405
 ENTRY DATE: Entered STN: 20040421
 Last Updated on STN: 20040521
 Entered Medline: 20040520
 AB With the ageing of the population in industrial countries, osteoporosis became an important concern of public health. For an efficacious treatment of this disease, we would need drugs capable of selectively and safely increasing bone volume. Recent genetic analyses revealed a new signaling pathway involved in the regulation of osteoblastic cells and the acquisition of pic bone mass. Loss or gain of function mutations in the ***LRP5*** gene have been found to be associated with correspondingly low or high bone mass syndromes. Loss of function is associated with juvenile osteoporosis, whereas gain of function leads to the high bone mass syndrome. Recent studies have shown that ***LRP5*** is implicated in the regulation of the proliferation and of the activity of osteoblastic cells. By analogy with other cellular systems, it has been suggested that ***LRP5*** plays a role in the Wnt signaling system. Wnt proteins are known to be involved in developmental processes and the implication of this system in controlling osteoblastic activity and bone formation was completely unexpected. Analysis of the cellular mechanism by which Wnt/ ***LRP5*** activates osteoblastic cells is of potential interest for the development of new molecules capable of selectively increasing bone mass for the treatment of osteoporosis.

L5 ANSWER 25 OF 45 MEDLINE on STN
 DUPLICATE 3
 ACCESSION NUMBER: 2004505926 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15474285
 TITLE: Wnt signaling in ***osteoblasts*** and bone diseases.
 AUTHOR: Westendorf Jennifer J; Kahler Rachel A; Schroeder Tania M
 CORPORATE SOURCE: The Cancer Center and Department of Orthopaedic Surgery,

University of Minnesota, MMC 806, 420
Delaware St. SE,
Minneapolis, MN 55455, USA..
weste047@umn.edu
SOURCE: Gene, (2004 Oct 27) 341 19-39. Ref:
219

Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20050114
Entered Medline: 20050113

AB Recent revelations that the canonical Wnt
signaling pathway promotes
postnatal bone accrual are major advances in our
understanding of skeletal
biology and bring tremendous promise for new
therapeutic treatments for
osteoporosis and other diseases of altered bone
mass. Wnts are soluble
glycoproteins that engage receptor complexes
composed of ***Lrp5*** /6
and Frizzled proteins. A subgroup of Wnts induces
a cascade of
intracellular events that stabilize beta-catenin,
facilitating its
transport to nuclei where it binds Lef1/Tcf
transcription factors and
alters gene expression to promote osteoblast
expansion and function.
Natural extracellular Wnt antagonists, Dickkopfs and
secreted
frizzled-related proteins, impair osteoblast function
and block bone
formation. In several genetic disorders of altered
skeletal mass,
mutations in ***LRP5*** create gain-of-function or
loss-of-function
receptors that are resistant to normal regulatory
mechanisms and cause
higher or lower bone density, respectively. In this
review, we summarize
the available molecular, cellular, and genetic data
that demonstrate how
Lrp5 and other components of the Wnt
signaling pathway influence
osteoblast proliferation, function, and survival. We
also discuss
regulatory mechanisms discovered in developmental
and tumor models that
may provide insights into novel therapies for bone
diseases.

L5 ANSWER 26 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2003:330153
USPATFULL
TITLE: Diagnosis, prognosis and
identification of potential
therapeutic targets of multiple myeloma
based on gene
expression profiling
INVENTOR(S): Shaughnessy, John D., Little
Rock, AR, UNITED STATES

Barlogie, Bart, Little Rock, AR, UNITED
STATES
Zhan, Fenghuang, Little Rock, AR,
UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2003232364 A1		
20031218		
APPLICATION INFO.: US 2003-409004 A1		
20030408 (10)		
RELATED APPLN. INFO.: Continuation-in-part of Ser.		
No. US 2002-289746, filed		
on 7 Nov 2002, PENDING		

NUMBER	DATE
PRIORITY INFORMATION: US 2002-403075P	
20020813 (60)	
US 2001-348238P	20011107 (60)
US 2002-355386P	20020208 (60)
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: Dr. Benjamin Adler,	
ADLER & ASSOCIATES, 8011 Candle	
Lane, Houston, TX, 77071	
NUMBER OF CLAIMS:	22
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	18 Drawing Page(s)
LINE COUNT:	4100
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB Gene expression profiling between normal B	
cells/plasma cells and	
multiple myeloma cells revealed four distinct	
subgroups of multiple	
myeloma plasma cells that have significant	
correlation with clinical	
characteristics known to be associated with poor	
prognosis. Diagnosis	
for multiple myeloma (and possibly monoclonal	
gammopathy of undetermined	
significance) based on differential expression of 14	
genes, as well as	
prognostics for the four subgroups of multiple	
myeloma based on the	
expression of 24 genes were also established.	
Gene expression profiling	
also allows placing multiple myeloma into a	
developmental schema	
parallel to that of normal plasma cell differentiation.	
The development	
of a gene expression- or developmental stage-	
based classification system	
for multiple myeloma would lead to rational design	
of more accurate and	
sensitive diagnostics, prognostics and tumor-	
specific therapies for	
multiple myeloma.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 27 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2003:312196
USPATFULL
TITLE: High bone mass gene of 11q13.3
INVENTOR(S): Carulli, John P., Southboro, MA,
UNITED STATES
Recker, Robert R., Omaha, NE, UNITED
STATES

Johnson, Mark L., Omaha, NE, UNITED STATES
Little, Randall D., Newtonville, MA, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2003219793 A1 20031127		
APPLICATION INFO.: US 2003-374979 A1 20030228 (10)		
RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-240851, filed on 4 Oct 2002, PENDING A 371 of International Ser. No. WO 2000-US16951, filed on 21 Jun 2000, PENDING A 371 of International Ser. No. US 2000-578900, filed on 26 May 2000, PENDING		
DOCUMENT TYPE: Utility		
FILE SEGMENT: APPLICATION		
LEGAL REPRESENTATIVE: Estelle J. Tsevdos, Esq., KENYON & KENYON, One Broadway, New York, NY, 10004		
NUMBER OF CLAIMS: 117		
EXEMPLARY CLAIM: 1		
NUMBER OF DRAWINGS: 31 Drawing Page(s)		
LINE COUNT: 5096		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
AB The present invention relates to methods and materials used to isolate and detect a high bone mass gene and a corresponding wild-type gene, and mutants thereof. The present invention also relates to the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The genes identified in the present invention are implicated in bone development and in focal adhesion signaling. The invention also provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
L5 ANSWER 28 OF 45 USPATFULL on STN		
ACCESSION NUMBER: 2003:237343		
USPATFULL		
TITLE: Wnt and frizzled receptors as targets for immunotherapy in head and neck squamous cell carcinomas		
INVENTOR(S): Rhee, Chae-Seo, Seoul, KOREA, REPUBLIC OF		
Sen, Malini, San Diego, CA, UNITED STATES		

Wu, Christina, San Diego, CA, UNITED STATES
Leoni, Lorenzo M., San Diego, CA, UNITED STATES
Corr, Maripat, San Diego, CA, UNITED STATES
Carson, Dennis A., Del Mar, CA, UNITED STATES
PATENT ASSIGNEE(S): REGENTS OF THE UNIVERSITY OF CALIFORNIA, Oakland, CA (non-U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 2003165500 A1 20030904		
APPLICATION INFO.: US 2002-285976 A1 20021101 (10)		
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2002-US13802, filed on 1 May 2002, PENDING		

NUMBER	DATE
PRIORITY INFORMATION: US 2001-287995P 20010501 (60)	
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834	
NUMBER OF CLAIMS: 140	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 33 Drawing Page(s)	
LINE COUNT: 7969	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The diverse receptor-ligand pairs of the Wnt and frizzled (Fzd) families play important roles during embryonic development, and thus may be overexpressed in cancers that arise from immature cells. The mRNA levels and expression levels of 5 Wnt (Wnt-1, 5a, 7a, 10b, 13) and 2 Fzd (Fzd-2, 5) genes in 10 head and neck squamous carcinoma cell lines (HNSCC) were investigated. In addition, anti-Wnt-1 antibodies were used to study the Wnt/Fzd signalling pathway. These results indicate that HNSCC cell lines overexpress one or more Wnt and Fzd genes, and the proliferation and survival of a subset of HNSCC may depend on the Wnt/Fzd pathway. Therefore, the Wnt and Fzd receptors may be useful targets for immunotherapy of this common cancer.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 29 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2003:187400
USPATFULL
TITLE: Compositions and methods for modulating blood-brain barrier transport
INVENTOR(S): Beliveau, Richard, Quebec, CANADA

Demeule, Michel, Montreal, CANADA
Yang, Joseph, North Delta, CANADA
Kennard, Malcolm L., North Vancouver,
CANADA
Gabathuler, Reinhard, Vancouver,
CANADA
PATENT ASSIGNEE(S): BioMarin Pharmaceutical
Inc., Novato, CA (non-U.S.
corporation)

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003129186	A1
20030710		
APPLICATION INFO.:	US 2002-206448	A1
20020725 (10)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2001-308002P
20010725 (60)	
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS:	28
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	44 Drawing Page(s)
LINE COUNT:	3332
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB	This invention provides conjugates of therapeutic or active agents with melanotransferrin or with other ligands of a melanotransferrin receptor, melanotransferrin receptor modulators, and related compositions and methods for modulating blood-brain barrier transport by providing methods of screening and selecting such conjugates, ligands, and modulators in vitro and in vivo, and methods of use of such conjugates, modulators and ligands in diagnosis and the treatment of diseases, including particularly diseases of the central nervous system or lysosomal storage diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 30 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2003:173952
USPATFULL
TITLE: Bone anabolic compounds and
methods of use
INVENTOR(S): Manolagas, Stavros C., Little
Rock, AR, UNITED STATES
Katzenellenbogen, John A., Urbana, IL,
UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003119800	A1
20030626		
APPLICATION INFO.:	US 2002-165380	A1
20020607 (10)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2001-299009P
20010618 (60)	
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	KNOBBE MARTENS OLSON & BEAR LLP, 2040 MAIN STREET, FOURTEENTH FLOOR, IRVINE, CA, 92614
NUMBER OF CLAIMS:	84
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	31 Drawing Page(s)
LINE COUNT:	3219
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB	A variety of bone anabolic compounds are useful for maintaining and/or increasing bone mass, density, and/or strength in mammals. Preferred compounds enhance bone anabolic activity while minimizing or eliminating undesirable feminizing or masculinizing effects.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 31 OF 45 USPATFULL on STN
ACCESSION NUMBER: 2003:37506 USPATFULL
TITLE: Regulator gene and system useful for
the diagnosis and
therapy of osteoporosis
INVENTOR(S): Warman, Matthew L., Shaker
Heights, OH, UNITED STATES
Gong, Yaoqin, Jinan, CHINA
Olsen, Bjorn R., Milton, MA, UNITED

STATES
Rawadi, Georges, Paris, FRANCE
Roman-Roman, Sergio, Paris, FRANCE

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003027151	A1
20030206		
APPLICATION INFO.:	US 2001-931375	A1
20010817 (9)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2001-304851P
20010713 (60)	
	US 2000-226119P 20000818 (60)
	US 2000-234337P 20000922 (60)
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HELLER EHRMAN WHITE & MCAULIFFE LLP, 1666 K STREET,NW, SUITE 300, WASHINGTON, DC, 20006
NUMBER OF CLAIMS:	36
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	16 Drawing Page(s)
LINE COUNT:	3896
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB	A bone strength and mineralization regulatory ("BSMR") protein is provided that can exist in multiple forms and that affects bone density. Polymorphic gene sequences of the protein are provided that are diagnostic of predipostion to osteoporosis. Other detection tools,

compositions and methods of their use also are provided for predicting, evaluating and altering bone strength and mineralization status. The invention provides new natural and synthetic pharmaceuticals that effect the BSMR regulatory pathway and improve bone status. Tools also are provided for finding new pharmaceuticals that operate by binding to BSMR and that activate and/or deactivate this protein's biological function related to osteoporosis and blood vessel formation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 32 OF 45 MEDLINE on STN
 DUPLICATE 4
 ACCESSION NUMBER: 2003149709 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12551949
 TITLE: Lymphoid enhancer factor-1 and beta-catenin inhibit Runx2-dependent transcriptional activation of the osteocalcin promoter.
 AUTHOR: Kahler Rachel A; Westendorf Jennifer J
 CORPORATE SOURCE: University of Minnesota Cancer Center, Department of Orthopaedic Surgery and Graduate Program in Microbiology, Immunology and Cancer Biology, Minneapolis, Minnesota 55455, USA.
 SOURCE: Journal of biological chemistry, (2003 Apr 4) 278 (14) 11937-44.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200305
 ENTRY DATE: Entered STN: 20030401
 Last Updated on STN: 20030520
 Entered Medline: 20030519
 AB Functional control of the transcription factor Runx2 is crucial for normal bone formation. Runx2 is detectable throughout osteoblast development and maturation and temporally regulates several bone-specific genes. In this study, we identified a novel post-translational mechanism regulating Runx2-dependent activation of the osteocalcin promoter. A functional binding site for the high mobility group protein lymphoid enhancer-binding factor 1 (LEF1) was found adjacent to the proximal Runx2-binding site in the osteocalcin promoter. In transcription assays, LEF1 repressed Runx2-induced activation of the mouse osteocalcin 2 promoter in several osteoblast lineage cell lines. Mutations in the LEF1-binding site increased the basal activity of the osteocalcin promoter; however, the

LEF1 recognition site in the osteocalcin promoter was surprisingly not required for LEF1 repression. A novel interaction between the DNA-binding domains of Runx2 and LEF1 was identified and found crucial for LEF1-mediated repression of Runx2. LEF1 is a nuclear effector of the Wnt/ ***LRP5*** /beta-catenin signaling pathway, which is also essential for osteoblast proliferation and normal skeletal development. A constitutively active beta-catenin enhanced LEF1-dependent repression of Runx2. These data identify a novel mechanism of regulating Runx2 activity in ***osteoblasts*** and link Runx2 transcriptional activity to beta-catenin signaling.

L5 ANSWER 33 OF 45 MEDLINE on STN
 DUPLICATE 5
 ACCESSION NUMBER: 2003508144 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14584895
 TITLE: BMP-2 controls alkaline phosphatase expression and osteoblast mineralization by a Wnt autocrine loop.
 AUTHOR: Rawadi Georges; Vayssiere Beatrice; Dunn Fred; Baron Roland; Roman-Roman Sergio
 CORPORATE SOURCE: Proskelia Pharmaceuticals, Romainville, France..
 georges.rawadi@proskelia.com
 SOURCE: Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2003 Oct) 18 (10) 1842-53.
 Journal code: 8610640. ISSN: 0884-0431.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200406
 ENTRY DATE: Entered STN: 20031031
 Last Updated on STN: 20040603
 Entered Medline: 20040602
 AB Wnt/beta-catenin signaling has recently been suggested to be involved in bone biology. The precise role of this cascade in osteoblast differentiation was examined. We show that a Wnt autocrine loop mediates the induction of alkaline phosphatase and mineralization by BMP-2 in pre-osteoblastic cells. INTRODUCTION: Loss of function of ***LRP5*** leads to osteoporosis (OPPG syndrome), and a specific point mutation in this same receptor results in high bone mass (HBM). Because ***LRP5*** acts as a coreceptor for Wnt proteins, these findings suggest a crucial role for Wnt signaling in bone biology. MATERIALS AND METHODS: We have investigated the involvement of the Wnt/ ***LRP5*** cascade in

osteoblast function by using the pluripotent mesenchymal cell lines C3H10T1/2, C2C12, and ST2 and the osteoblast cell line MC3T3-E1.

Transfection experiments were carried out with a number of elements of the Wnt/ *****LRP5***** pathway. Measuring osteoblast and adipocyte differentiation markers addressed the effect of this cascade on osteoblast differentiation. RESULTS: In mesenchymal cells, only Wnt's capable of stabilizing beta-catenin induced the expression of alkaline phosphatase (ALP). Wnt3a-mediated ALP induction was inhibited by overexpression of either Xddl, dickkopf 1 (dkk1), or LRP5deltaC, indicating that canonical beta-catenin signaling is responsible for this activity. The use of Noggin, a bone morphogenic protein (BMP) inhibitor, or cyclopamine, a Hedgehog inhibitor, revealed that the induction of ALP by Wnt is independent of these morphogenetic proteins and does not require de novo protein synthesis. In contrast, blocking Wnt/ *****LRP5***** signaling or protein synthesis inhibited the ability of both BMP-2 and Shh to induce ALP in mesenchymal cells. Moreover, BMP-2 enhanced Wnt1 and Wnt3a expression in our cells. In MC3T3-E1 cells, where endogenous ALP levels are maximal, antagonizing the Wnt/ *****LRP5***** pathway led to a decrease of ALP activity. In addition, overexpression of dkk1 reduced extracellular matrix mineralization in a BMP-2-dependent assay. CONCLUSIONS: Our data strongly suggest that the capacity of BMP-2 and Shh to induce ALP relies on Wnt expression and the Wnt/ *****LRP5***** signaling cascade. Moreover the effects of BMP-2 on extracellular matrix mineralization by *****osteoblasts***** are mediated, at least in part, by the induction of a Wnt autocrine/paracrine loop. These results may help to explain the phenotype of OPG patients and HBM.

L5 ANSWER 34 OF 45 MEDLINE on STN
DUPLICATE 6

ACCESSION NUMBER: 2003290363 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12817748
TITLE: High bone mass in mice expressing a mutant *****LRP5***** gene.

AUTHOR: Babij Philip; Zhao Weiguang; Small Clayton; Kharode

Yogendra; Yaworsky Paul J; Bouxsein Mary L; Reddy

Padmalatha S; Bodine Peter V N;

Robinson John A; Bhat

Bheem; Marzolf James; Moran Robert A; Bex Frederick

CORPORATE SOURCE: Genomics, Wyeth Research, Andover, Massachusetts, USA.

SOURCE: Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2003 Jun) 18 (6) 960-74.

Journal code: 8610640. ISSN: 0884-0431.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200402

ENTRY DATE: Entered STN: 20030624

Last Updated on STN: 20040212

Entered Medline: 20040211

AB A unique mutation in *****LRP5***** is associated with high bone mass in man. Transgenic mice expressing this *****LRP5***** mutation have a similar phenotype with high bone mass and enhanced strength. These results underscore the importance of *****LRP5***** in skeletal regulation and suggest targets for therapies for bone disease. A mutation (G171V) in the low-density lipoprotein receptor related protein 5 (*****LRP5*****) has been associated with high bone mass (HBM) in two independent human kindreds. To validate the role of the mutation, several lines of transgenic mice were created expressing either the human *****LRP5*****

G171V substitution or the wildtype *****LRP5***** gene in bone.

Volumetric bone mineral density (vBMD) analysis by pQCT showed dramatic increases in both total vBMD (30-55%) and trabecular vBMD (103-250%) of the distal femoral metaphysis and increased cortical size of the femoral diaphysis in mutant G171V transgenics at 5, 9, 17, 26, and 52 weeks of age (p < 0.01 for all). In addition, high-resolution microcomputed tomography (microCT) analysis of the distal femorae and lumbar vertebrae revealed an increase (110-232%) in trabecular bone volume fraction caused by both increased trabecular number (41-74%) and increased trabecular thickness (34-46%; p < 0.01 for all) in the mutant G171V mice. The increased bone

mass was associated with significant increases in vertebral compressive strength (80-140%) and the increased cortical size with significant increases in femoral bending strength (50-130%). There were no differences in osteoclast number at 17 weeks of age. However, compared with littermate controls, the mutant G171V transgenic mice showed an increase in actively mineralizing bone surface, enhanced alkaline phosphatase staining in *****osteoblasts*****, and a significant reduction in the number of TUNEL-positive *****osteoblasts***** and osteocytes.

These results suggest that the increased bone mineral density in mutant G171V mice was caused by increased numbers of active ***osteoblasts***, which could in part be because of their increased functional lifespan. While slight bone anabolic activity was observed from overexpression of the wildtype ***LRP5*** gene, it is clear that the G171V mutation, rather than overexpression of the receptor itself, is primarily responsible for the dramatic HBM bone effects. Together, these findings establish the importance of this novel and unexpected role of a lipoprotein receptor in regulating bone mass and afford a new model to explore ***LRP5*** and its recent association with Wnt signaling in bone biology.

L5 ANSWER 35 OF 45 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2003:114750 BIOSIS
 DOCUMENT NUMBER: PREV200300114750
 TITLE: IGF-I and IGFBP-3 transport in the rat heart.
 AUTHOR(S): Boes, Mary; Dake, Brian L.; Booth, Barbara A.; Sandra, Alexander; Bateman, Mathew; Knudtson, Kevin L.; Bar, Robert S. [Reprint Author]
 CORPORATE SOURCE: Division of Endocrinology, Dept. of Internal Medicine, Univ. of Iowa, Highway 6 West, 3E19 VA Medical Center, Iowa City, IA, 52246, USA
 SOURCE: American Journal of Physiology, (January 2003) Vol. 284, No. 1 Part 1, pp. E237-E239. print. ISSN: 0002-9513 (ISSN print).
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 26 Feb 2003
 Last Updated on STN: 26 Feb 2003
 AB Specific binding of IGF-binding protein (IGFBP)-3 was shown to be present in the isolated, beating rat heart. The uptake of perfused 125I-labeled IGF-I in the beating heart was decreased to 9% by blocking IGF-I binding sites with the IGF-I analog Long R3 (***LR3***) IGF-I. When ***LR3*** was perfused with complexes of 125I-IGF-IcndotIGFBP-3, uptake of 125I-IGF-I was decreased to 41%, which was significantly greater than ***LR3*** and 125I-IGF-I (41 vs. 9%). These data suggest that both microvessel IGF-I and IGFBP-3 binding sites contribute to the transport of IGF-I in the perfused rat heart. This also suggests a novel and plausible mechanism whereby circulating IGFs reach sites of IGF bioactivity.

L5 ANSWER 36 OF 45 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2003:507666 BIOSIS
 DOCUMENT NUMBER: PREV200300509318
 TITLE: Regulation of bone formation by Wnt signaling.
 AUTHOR(S): Patel, M. S. [Reprint Author]; Glass, D. A. II [Reprint Author]; Long, F.; Taketo, M. M.; McMahon, A. P.; Karsenty, G. [Reprint Author]
 CORPORATE SOURCE: Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
 SOURCE: American Journal of Human Genetics, (November 2003) Vol. 73, No. 5, pp. 171. print.
 Meeting Info.: 53rd Annual Meeting of the American Society of Human Genetics. Los Angeles, CA, USA. November 04-08, 2003. American Society of Human Genetics.
 CODEN: AJHGAG. ISSN: 0002-9297.
 DOCUMENT TYPE: Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 29 Oct 2003
 Last Updated on STN: 29 Oct 2003

L5 ANSWER 37 OF 45 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
 ACCESSION NUMBER: 2002:517776 BIOSIS
 DOCUMENT NUMBER: PREV200200517776
 TITLE: High bone density due to a mutation in ***LDL*** - ***receptor*** - ***related*** ***protein***
 5 : The authors reply.
 AUTHOR(S): Boyden, Lynn [Reprint author]; Insogna, Karl [Reprint author]; Lifton, Richard P. [Reprint author]
 CORPORATE SOURCE: Yale University School of Medicine, New Haven, CT, 06510, USA
 SOURCE: New England Journal of Medicine, (September 19, 2002) Vol. 347, No. 12, pp. 944. print.
 CODEN: NEJMAG. ISSN: 0028-4793.
 DOCUMENT TYPE: Letter
 LANGUAGE: English
 ENTRY DATE: Entered STN: 9 Oct 2002
 Last Updated on STN: 9 Oct 2002

L5 ANSWER 38 OF 45 USPATFULL on STN
 ACCESSION NUMBER: 2002:301758
 USPATFULL
 TITLE: Transgenic mice containing LPR5 gene disruptions
 INVENTOR(S): Klein, Robert, Palo Alto, CA, UNITED STATES

NUMBER	KIND	DATE
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PATENT INFORMATION:	US 2002169307	A1
	20021114	

APPLICATION INFO.: US 2001-887540 A1
20010621 (9)

NUMBER DATE

PRIORITY INFORMATION: US 2000-213201P
20000621 (60)

US 2000-223123P 20000807 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: DELTAGEN, INC., 1003
Hamilton Avenue, Menlo Park, CA,
94025

NUMBER OF CLAIMS: 16

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 9 Drawing Page(s)

LINE COUNT: 2105

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to transgenic animals, as well as compositions and methods relating to the characterization of gene function. Specifically, the present invention provides transgenic mice comprising mutations in a low density lipoprotein-related protein 5 gene. Such transgenic mice are useful as models for disease and for identifying agents that modulate gene expression and gene function, and as potential treatments for various disease states and disease conditions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 39 OF 45 MEDLINE on STN
DUPLICATE 7

ACCESSION NUMBER: 2002219603 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11956231

TITLE: Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in *****Lrp5*****, a Wnt coreceptor.

AUTHOR: Kato Masaki; Patel Millan S; Levasseur Regis; Lobov Ivan; Chang Benny H-J; Glass Donald A 2nd; Hartmann Christine; Li Lan; Hwang Tae-Ho; Brayton Cory F; Lang Richard A; Karsenty Gerard; Chan Lawrence
CORPORATE SOURCE: Department of Molecular and Cellular Biology and Medicine, Baylor College of Medicine, Houston, TX 77030, USA.

CONTRACT NUMBER: AR42919 (NIAMS)

DE11290 (NIDCR)

DK58882 (NIDDK)

HL16512 (NHLBI)

HL51586 (NHLBI)

SOURCE: Journal of cell biology, (2002 Apr 15) 157 (2) 303-14.

Journal code: 0375356. ISSN: 0021-9525.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Space Life Sciences

ENTRY MONTH: 200205

ENTRY DATE: Entered STN: 20020417

Last Updated on STN: 20030105

Entered Medline: 20020516

AB The low-density lipoprotein receptor-related protein (Lrp)-5 functions as a Wnt coreceptor. Here we show that mice with a targeted disruption of

*****Lrp5***** develop a low bone mass phenotype.

In vivo and in vitro analyses indicate that this phenotype becomes evident postnatally, and demonstrate that it is secondary to decreased osteoblast proliferation and

function in a Cbfa1-independent manner.

*****Lrp5***** is expressed in *****osteoblasts***** and is required for optimal Wnt signaling in *****osteoblasts*****. In addition, *****Lrp5***** -

deficient mice display persistent embryonic eye vascularization due to a failure of macrophage-induced endothelial cell apoptosis.

These results implicate Wnt proteins in the postnatal control of vascular regression and bone formation, two functions affected in many diseases. Moreover, these features recapitulate human osteoporosis-pseudoglioma syndrome, caused by *****LRP5***** inactivation.

L5 ANSWER 40 OF 45 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:795757 CAPLUS

DOCUMENT NUMBER: 138:83661

TITLE: Insulin receptor substrate-2 maintains predominance of anabolic function over catabolic function of *****osteoblasts*****

AUTHOR(S): Akune, Toru; Ogata, Naoshi; Hoshi, Kazuto; Kubota, Naoto; Terauchi, Yasuo; Tobe, Kazuyuki; Takagi, Hideko; Azuma, Yoshiaki; Kadowaki, Takashi; Nakamura, Kozo; Kawaguchi, Hiroshi

CORPORATE SOURCE: Department of Orthopaedic Surgery, University of Tokyo, Tokyo, 113-8655, Japan
SOURCE: Journal of Cell Biology (2002), 159(1), 147-156

CODEN: JCLBA3; ISSN: 0021-9525

PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insulin receptor substrates (IRS-1 and IRS-2) are essential for intracellular signaling by insulin and insulin-like growth factor-I (IGF-I), anabolic regulators of bone metab.

Although mice lacking the IRS-2 gene (IRS-2^{-/-} mice) developed normally, they exhibited osteopenia with decreased bone formation and increased bone resorption. Cultured

IRS-2/- ***osteoblasts*** showed reduced differentiation and matrix synthesis compared with wild-type ***osteoblasts***. However, they showed increased receptor activator of nuclear factor .kappa.B ligand (RANKL) expression and osteoclastogenesis in the coculture with bone marrow cells, which were restored by reintroduction of IRS-2 using an adenovirus vector. Although IRS-2 was expressed and phosphorylated by insulin and IGF-I in both ***osteoblasts*** and osteoclastic cells, cultures in the absence of ***osteoblasts*** revealed that intrinsic IRS-2 signaling in osteoclastic cells was not important for their differentiation, function, or survival. It is concluded that IRS-2 deficiency in ***osteoblasts*** causes osteopenia through impaired anabolic function and enhanced supporting ability of osteoclastogenesis. We propose that IRS-2 is needed to maintain the predominance of bone formation over bone resorption, whereas IRS-1 maintains bone turnover, as we previously reported; the integration of these two signalings causes a potent bone anabolic action by insulin and IGF-I.

REFERENCE COUNT: 50 THERE ARE 50
CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS
AVAILABLE IN THE RE FORMAT

L5 ANSWER 41 OF 45 MEDLINE on STN
DUPLICATE 8
ACCESSION NUMBER: 2001673198 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11719191
TITLE: ***LDL*** ***receptor*** -
related
protein ***5*** (***LRP5***)
affects bone
accrual and eye development.

AUTHOR: Gong Y; Slee R B; Fukai N; Rawadi G; Roman-Roman S;
Reginato A M; Wang H; Cundy T; Glorieux F H; Lev D;
Zacharin M; Oexle K; Marcelino J; Suwairi W; Heeger S;
Sabatakos G; Apte S; Adkins W N;
Allgrove J;
Arslan-Kirchner M; Batch J A; Beighton P;
Black G C; Boles R G; Boon L M; Borrone C; Brunner H G;
Carle G F;
Dallapiccola B; De Paepe A; Floege B;
Halfhide M L; Hall B;
Hennekam R C; Hirose T; Jans A; Juppner H; Kim C A;
Keppler-Noreuil K; Kohlschuetter A;
LaCombe D; Lambert M;
Lemyre E; Letteboer T; Peltonen L;
Ramesar R S; Romanengo M; Somer H; Steichen-Gersdorf E;
Steinmann B; Sullivan B;
Superti-Furga A; Swoboda W; van den Boogaard M J; Van Hul

W; Vikkula M; Votruba M; Zabel B; Garcia T; Baron R; Olsen B R; Warman M L
CORPORATE SOURCE: Osteoporosis-Pseudoglioma Syndrome Collaborative Group.
SOURCE: Cell, (2001 Nov 16) 107 (4) 513-23.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011126
Last Updated on STN: 20030403
Entered Medline: 20020108

AB In humans, low peak bone mass is a significant risk factor for osteoporosis. We report that ***LRP5***, encoding the low-density lipoprotein receptor-related protein 5, affects bone mass accrual during growth. Mutations in ***LRP5*** cause the autosomal recessive disorder osteoporosis-pseudoglioma syndrome (OPPG). We find that OPPG carriers have reduced bone mass when compared to age- and gender-matched controls. We demonstrate ***LRP5*** expression by ***osteoblasts*** in situ and show that ***LRP5*** can transduce Wnt signaling in vitro via the canonical pathway. We further show that a mutant-secreted form of ***LRP5*** can reduce bone thickness in mouse calvarial explant cultures. These data indicate that Wnt-mediated signaling via ***LRP5*** affects bone accrual during growth and is important for the establishment of peak bone mass.

L5 ANSWER 42 OF 45 BIOSIS COPYRIGHT (c)
2005 The Thomson Corporation. on
STN
ACCESSION NUMBER: 2001:546888 BIOSIS
DOCUMENT NUMBER: PREV200100546888
TITLE: Human bone mass accrual is affected by mutations in the low density lipoprotein receptor-related protein 5 gene (***LRP5***).
AUTHOR(S): Gong, Y. [Reprint author]; Slee, R. [Reprint author];
Osteoporosis-Pseudoglioma Collaborative Group
CORPORATE SOURCE: Department of Genetics and Center for Human Genetics, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH, USA
SOURCE: American Journal of Human Genetics, (October, 2001) Vol. 69, No. 4 Supplement, pp. 189. print.
Meeting Info.: 51st Annual Meeting of the American Society of Human Genetics. San Diego, California, USA. October 12-16, 2001.

CODEN: AJHGAG. ISSN: 0002-9297.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Nov 2001
Last Updated on STN: 25 Feb 2002

L5 ANSWER 43 OF 45 MEDLINE on STN
DUPLICATE 9
ACCESSION NUMBER: 1999008902 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9790987
TITLE: Molecular cloning and characterization
of ***LR3***, a

novel LDL receptor family protein with
mitogenic activity.
AUTHOR: Dong Y; Lathrop W; Weaver D; Qiu
Q; Cini J; Bertolini D;
Chen D

CORPORATE SOURCE: Pharmaceutical Division,
Bayer Corporation, West Haven,
Connecticut, 06516-4175, USA.

SOURCE: Biochemical and biophysical
research communications, (1998
Oct 29) 251 (3) 784-90.

Journal code: 0372516. ISSN: 0006-291X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AF077820

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981203

AB We report molecular cloning and initial functional
characterization of a
novel member of the low density lipoprotein receptor
(LDLR) gene family.

The cDNA was isolated from a human osteoblast
cDNA library and encoded a
1,615 amino acids protein designated as ***LR3***

. It has, in the
extracellular region, a cluster of three LDLR ligand
binding repeats at a
juxtamembrane position and four EGF precursor
homology domains separated
by YWTD spacer repeats. The entire ectodomain
shares the same modular

organization with the middle portion of the
extracellular regions of two
LDLR family members, LDLR-related protein (LRP),
and gp330/megalin.

LR3 mRNA was expressed in most of the
adult and fetal tissues
examined. The highest expression level was seen
in aorta. In human

osteosarcoma cells examined, ***LR3*** mRNA
was highly enriched in
TE85 cells, moderately expressed in MG63 cells and
primary human

osteoblasts, and undetectable in SaOS-2
cells. NIH 3T3 cells
transfected with either full length ***LR3*** or its
ectodomain showed
significantly increased proliferation, whereas
transfection of

intracellular domain had no proliferative effect. We
predict that

LR3 is a multi-functional protein with
potential mitogenic
activity.
Copyright 1998 Academic Press.

L5 ANSWER 44 OF 45 BIOSIS COPYRIGHT (c)
2005 The Thomson Corporation. on
STN

ACCESSION NUMBER: 1999:463 BIOSIS
DOCUMENT NUMBER: PREV199900000463
TITLE: Molecular cloning and characterization
of ***LR3***, a

novel LDL receptor family protein with
mitogenic activity.

AUTHOR(S): Dong, Yu; Lathrop, William;
Weaver, Daniel; Qiu, Qingqing;
Cini, John; Bertolini, Donald; Chen, David
CORPORATE SOURCE: Bayer Res. Cent.,
Pharmaceutical Div., Bayer Corporation,
400 Morgan Lane, West Haven, CT 06516-
4175, USA

SOURCE: Biochemical and Biophysical
Research Communications, (Oct.
29, 1998) Vol. 25, No. 3, pp. 784-790.

print.

CODEN: BBRA9. ISSN: 0006-291X.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 11 Jan 1999
Last Updated on STN: 11 Jan 1999

AB We report molecular cloning and initial functional
characterization of a
novel member of the low density lipoprotein receptor
(LDLR) gene family.

The cDNA was isolated from a human osteoblast
cDNA library and encoded a
1,615 amino acids protein designated as ***LR3***

. It has, in the
extracellular region, a cluster of three LDLR ligand
binding repeats at a
juxtamembrane position and four EGF precursor
homology domains separated
by YWTD spacer repeats. The entire ectodomain
shares the same modular
organization with the middle portion of the
extracellular regions of two
LDLR family members, LDLR-related protein (LRP),
and gp330/megalin.

LR3 mRNA was expressed in most of the
adult and fetal tissues
examined. The highest expression level was seen
in aorta. In human
osteosarcoma cells examined, ***LR3*** mRNA
was highly enriched in
TE85 cells, moderately expressed in MG63 cells and
primary human

osteoblasts, and undetectable in SaOS-2
cells. NIH 3T3 cells
transfected with either full length ***LR3*** or its
ectodomain showed
significantly increased proliferation, whereas
transfection of
intracellular domain had no proliferative effect. We
predict that

LR3 is a multifunctional protein with potential
mitogenic
activity.

L5 ANSWER 45 OF 45 USPATFULL on STN
ACCESSION NUMBER: 97:109875 USPATFULL

TITLE: Endothelin antagonistic peptide derivatives
 INVENTOR(S): Ishikawa, Kiyofumi, Tokyo, Japan
 Fukami, Takehiro, Tokyo, Japan
 Hayama, Takashi, Tokyo, Japan
 Niiyama, Kenji, Tokyo, Japan
 Nagase, Toshio, Tokyo, Japan
 Mase, Toshiaki, Tokyo, Japan
 Fujita, Kagari, Tokyo, Japan
 Ihara, Masaki, Tokyo, Japan
 Ikemoto, Fumihiko, Tokyo, Japan
 Yano, Mitsuo, Tokyo, Japan
 PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Tokyo, Japan (non-U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 5691315		
19971125		
APPLICATION INFO.: US 1995-494818		
19950626 (8)		
RELATED APPLN. INFO.: Division of Ser. No. US 1994-213829, filed on 14 Mar 1994, now patented, Pat. No. US 5470833 which is a continuation of Ser. No. US 1992-884189, filed on 18 May 1992, now abandoned which is a division of Ser. No. US 1991-712095, filed on 7 Jun 1991, now abandoned		

NUMBER	DATE
PRIORITY INFORMATION: JP 1990-149105	
19900607	
DOCUMENT TYPE: Utility	
FILE SEGMENT: Granted	
PRIMARY EXAMINER: Tsang, Cecilia J.	
ASSISTANT EXAMINER: Marshall, S. G.	
LEGAL REPRESENTATIVE: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.	
NUMBER OF CLAIMS: 11	
EXEMPLARY CLAIM: 1	
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 4 Drawing Page(s)	
LINE COUNT: 5461	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	
AB The invention relates to compounds which are antagonists of endothelin, to processes for their preparation, and to their use as pharmaceuticals.	
The compounds of the invention are Useful in the treatment of hypertension, pulmonary hypertension, Reynaud's disease, myocardial infarction, angina pectoris, acute renal failure, cerebral infarction, cerebral vasospasm, arteriosclerosis, asthma, endotoxin shock, endotoxin-induced multiple organ failure or disseminated intravascular coagulation, and/or cyclosporin-induced renal failure or hypertension.	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	

=> s l1 and l3
 L6 120 L1 AND L3
 => duplicate remove l6
 DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, BIOTECHNO, USPATFULL'
 KEEP DUPLICATES FROM MORE THAN ONE FILE?
 Y/(N):n
 PROCESSING COMPLETED FOR L6
 L7 68 DUPLICATE REMOVE L6 (52 DUPLICATES REMOVED)
 => d l7 1- ibib,abs
 YOU HAVE REQUESTED DATA FROM 68 ANSWERS
 - CONTINUE? Y/(N):y

L7 ANSWER 1 OF 68 MEDLINE on STN
 DUPLICATE 1
 ACCESSION NUMBER: 2004616725 IN-PROCESS
 DOCUMENT NUMBER: PubMed ID: 15576404
 TITLE: Sequential roles of Hedgehog and Wnt signaling in osteoblast development.
 AUTHOR: Hu Hongliang; Hilton Matthew J; Tu Xiaolin; Yu Kai; Ornitz David M; Long Fanxin
 CORPORATE SOURCE: Department of Medicine, Washington University Medical School, St. Louis, MO 63110, USA.
 CONTRACT NUMBER: 5T32AR07033 (NIAMS) DK065789 (NIDDK) HD39952 (NICHD)
 SOURCE: Development (Cambridge, England), (2005 Jan) 132 (1) 49-60.
 Journal code: 8701744. ISSN: 0950-1991.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
 ENTRY DATE: Entered STN: 20041220
 Last Updated on STN: 20050204
 AB Signals that govern development of the osteoblast lineage are not well understood. Indian hedgehog (Ihh), a member of the hedgehog (Hh) family of proteins, is essential for osteogenesis in the endochondral skeleton during embryogenesis. The canonical pathway of Wnt signaling has been implicated by studies of ***Lrp5***, a co-receptor for ***Wnt*** proteins, in postnatal bone mass homeostasis. In the present study we demonstrate that beta-catenin, a central player in the canonical Wnt pathway, is indispensable for osteoblast differentiation in the mouse embryo. Moreover, we present evidence that Wnt signaling functions downstream of Ihh in development of the osteoblast lineage. Finally Wnt7b is identified as a potential endogenous ligand regulating osteogenesis. These data support a model that integrates Hh and Wnt signaling in the regulation of osteoblast development.

L7 ANSWER 2 OF 68 USPATFULL on STN
 ACCESSION NUMBER: 2004:309387
 USPATFULL
 TITLE: Transgenic animal model of bone mass modulation
 INVENTOR(S): Askew, G. Roger, Boxford, MA, UNITED STATES
 Babij, Philip, Dunstable, MA, UNITED STATES
 Bex, Frederick James, III, Newtown Square, PA, UNITED STATES
 Nest Bodine, Peter Van, Havertown, PA, UNITED STATES
 PATENT ASSIGNEE(S): Wyeth, Madison, NJ, UNITED STATES, 07940 (U.S. corporation)

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004244069 A1 20041202		
APPLICATION INFO.: US 2003-680287 A1 20031008 (10)		
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2002-US14876, filed on 13 May 2002, PENDING		

NUMBER	DATE
PRIORITY INFORMATION: US 2001-290071P 20010511 (60)	
US 2001-291311P	20010517 (60)
US 2002-353058P	20020201 (60)
US 2002-361293P	20020304 (60)
DOCUMENT TYPE: Utility	
FILE SEGMENT: APPLICATION	
LEGAL REPRESENTATIVE: BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404	
NUMBER OF CLAIMS:	44
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	61 Drawing Page(s)
LINE COUNT:	8213
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB The present invention relates to methods and materials used to express the HBM protein in animal cells and transgenic animals. The present invention also relates to transgenic animals expressing the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 68 USPATFULL on STN
 ACCESSION NUMBER: 2004:286719
 USPATFULL
 TITLE: Systems and methods for screening for modulators of neural differentiation
 INVENTOR(S): Jessel, Thomas, Bronx, NY, UNITED STATES
 Wichterle, Hynek, New York, NY, UNITED STATES
 Wilson, Sara I., New York, NY, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION: US 2004224887 A1 20041111		
APPLICATION INFO.: US 2004-789308 A1 20040226 (10)		
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-196882, filed on 16 Jul 2002, PENDING		
DOCUMENT TYPE: Utility		
FILE SEGMENT: APPLICATION		
LEGAL REPRESENTATIVE: Leslie Gladstone Restaino, Esq., Brown Raysman Millstein Felder & Steiner LLP, 163 Madison Avenue, P.O. Box 1989, Morristown, NJ, 07962-1989		
NUMBER OF CLAIMS:	80	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	16 Drawing Page(s)	
LINE COUNT:	4179	
CAS INDEXING IS AVAILABLE FOR THIS PATENT. AB The present invention provides in vitro systems for use in identifying modulators of neural differentiation. Also provided are modulators identified by these systems. The present invention further provides methods for identifying a modulator of neural differentiation, a modulator of a Wnt signalling pathway, a modulator of Wnt-dependent neural differentiation, a modulator of a BMP signalling pathway, a modulator of BMP-dependent neural differentiation, a modulator of a Hh signalling pathway, and a modulator of Hh-dependent neural differentiation. Also provided are modulators identified by these methods.		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 4 OF 68 USPATFULL on STN
 ACCESSION NUMBER: 2004:286140
 USPATFULL
 TITLE: Systems and methods for screening for modulators of neural differentiation
 INVENTOR(S): Jessel, Thomas, Bronx, NY, UNITED STATES
 Wichterle, Hynek, New York, NY, UNITED STATES
 Wilson, Sara, New York, NY, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004224302	A1
20041111		
APPLICATION INFO.:	US 2004-789266	A1
20040226 (10)		
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2002-196882, filed on 16 Jul 2002, PENDING	
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Leslie Gladstone Restaino, Esq., Brown Raysman Millstein Felder & Steiner LLP, 163 Madison Avenue, P.O. Box 1989, Morristown, NJ, 07962-1989	
NUMBER OF CLAIMS:	67	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	16 Drawing Page(s)	
LINE COUNT:	4051	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	AB The present invention provides in vitro systems for use in identifying modulators of neural differentiation. Also provided are modulators identified by these systems. The present invention further provides methods for identifying a modulator of neural differentiation, a modulator of an FGF signalling pathway, a modulator of FGF-dependent neural differentiation, a modulator of a retinoid signalling pathway, and a modulator of retinoid-dependent neural differentiation. Also provided are modulators identified by these methods.	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
L7 ANSWER 5 OF 68 USPATFULL on STN	ACCESSION NUMBER: 2004:282022	
USPATFULL	TITLE: Transgenic animal model of bone mass modulation	
INVENTOR(S):	Babji, Philip, Newbury Park, CA, UNITED STATES	
	Bex, Frederick James, Newton Square, PA, UNITED STATES	
	Bodine, Peter Van Nest, Havertown, PA, UNITED STATES	
	Askew, G. Roger, Boxford, MA, UNITED STATES	

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004221326	A1
20041104		
APPLICATION INFO.:	US 2004-477238	A1
20040412 (10)		
	WO 2002-US14876	20020513
PRIORITY INFORMATION:	US 2001-60290071	20010511
	US 2001-60291311	20010517
	US 2002-60353058	20020201

US 2002-60361293 20020304

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BURNS DOANE SWECKER & MATHIS L L P, POST OFFICE BOX 1404, ALEXANDRIA, VA, 22313-1404

NUMBER OF CLAIMS: 58

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 61 Drawing Page(s)

LINE COUNT: 7878

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and materials used to express the HBM protein in animal cells and transgenic animals. The present invention also relates to transgenic animals expressing the high bone mass gene, the corresponding wild-type gene, and mutants thereof. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 6 OF 68 USPATFULL on STN

ACCESSION NUMBER: 2004:221788

USPATFULL

TITLE: Protection of stem cells from cytotoxic agents by modulation of beta-catenin signaling pathways

INVENTOR(S): Weissman, Irving, Redwood City, CA, UNITED STATES

Reya, Tannishtha, Chapel Hill, NC, UNITED STATES

NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004171559	A1
20040902		
APPLICATION INFO.:	US 2003-729548	A1
20031205 (10)		

NUMBER	DATE
PRIORITY INFORMATION:	US 2002-431655P
20021206 (60)	
DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO PARK, CA, 94025
NUMBER OF CLAIMS:	25
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	9 Drawing Page(s)
LINE COUNT:	1784
CAS INDEXING IS AVAILABLE FOR THIS PATENT.	

AB Reagents that block the extracellular activation of .beta.-catenin are used to induce quiescence in normal stem cells, in order to reduce the killing of stem cells by anti-proliferative agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 7 OF 68 USPATFULL on STN
ACCESSION NUMBER: 2004:51429 USPATFULL
TITLE: Reagents and methods for modulating dkk-mediated interactions
INVENTOR(S): Allen, Kristina M., Hopkinton, MA, UNITED STATES
Anisowicz, Anthony, West Newton, MA, UNITED STATES
Damagnez, Veronique, Framingham, MA, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2004038860 A1
20040226

APPLICATION INFO.: US 2002-182936 A1
20020802 (10)

WO 2002-US15982 20020517

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BURNS DOANE

SWECKER & MATHIS L L P, POST OFFICE BOX
1404, ALEXANDRIA, VA, 22313-1404

NUMBER OF CLAIMS: 114

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 33 Drawing Page(s)

LINE COUNT: 5224

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides reagents, compounds, compositions, and methods relating to novel interactions of the extracellular domain of ***LRP5***, HBM (a variant of ***LRP5***), and/or LRP6 with Dkk, including Dkk-1. The various nucleic acids, polypeptides, antibodies, assay methods, diagnostic methods, and methods of treatment of the present invention are related to and impact on Dkk, ***LRP5***,

LRP6, HBM, and Wnt signaling. Dkk, ***LRP5***, LRP6, HBM, and Wnt are implicated in bone and lipid cellular signaling. Thus, the present invention provides reagents and methods for modulating lipid levels and/or bone mass and is useful in the treatment and diagnosis of abnormal lipid levels and bone mass disorders, such as osteoporosis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 8 OF 68 USPATFULL on STN
ACCESSION NUMBER: 2004:44501 USPATFULL
TITLE: Proteins and nucleic acids encoding same
INVENTOR(S): Tchernev, Velizar T., Branford, CT, UNITED STATES
Spytek, Kimberly A., New Haven, CT, UNITED STATES

Zerhusen, Bryan D., Branford, CT, UNITED STATES
Patturajan, Meera, Branford, CT, UNITED STATES
Shimkets, Richard A., West Haven, CT, UNITED STATES
Li, Li, Branford, CT, UNITED STATES
Gangolli, Esha A., Madison, CT, UNITED STATES
Padigaru, Muralidhara, Branford, CT, UNITED STATES
Anderson, David W., Branford, CT, UNITED STATES
Rastelli, Luca, Guilford, CT, UNITED STATES
Miller, Charles E., Hill Drive, CT, UNITED STATES
Gerlach, Valerie, Branford, CT, UNITED STATES
Taupier, Raymond J., JR., East Haven, CT, UNITED STATES
Gusev, Vladimir Y., UNITED STATES
Colman, Steven D., Guilford, CT, UNITED STATES
Wolenc, Adam Ryan, New Haven, CT, UNITED STATES
Pena, Carol E. A., Guilford, CT, UNITED STATES
Furtak, Katarzyna, Anosia, CT, UNITED STATES
Grosse, William M., Bransford, CT, UNITED STATES
Alsobrook, John P., II, Madison, CT, UNITED STATES
Lepley, Denise M., Branford, CT, UNITED STATES
Rieger, Daniel K., Branford, CT, UNITED STATES
Burgess, Catherine E., Wethersfield, CT, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2004033493 A1
20040219
APPLICATION INFO.: US 2002-72012 A1
20020131 (10)

NUMBER DATE

PRIORITY INFORMATION: US 2001-267459P
20010208 (60)

US 2001-266975P 20010207 (60)
US 2001-267057P 20010207 (60)
US 2001-266767P 20010205 (60)
US 2001-266406P 20010202 (60)
US 2001-265395P 20010131 (60)
US 2001-265412P 20010131 (60)
US 2001-265517P 20010131 (60)
US 2001-265514P 20010131 (60)
US 2001-267823P 20010209 (60)
US 2001-268974P 20010215 (60)
US 2001-271855P 20010227 (60)
US 2001-271839P 20010227 (60)
US 2001-273046P 20010302 (60)
US 2001-272788P 20010302 (60)
US 2001-275989P 20010314 (60)
US 2001-275925P 20010314 (60)
US 2001-275947P 20010314 (60)
US 2001-275950P 20010314 (60)

US 2001-276450P	20010315 (60)
US 2001-276448P	20010315 (60)
US 2001-276397P	20010316 (60)
US 2001-276768P	20010316 (60)
US 2001-278652P	20010320 (60)
US 2001-278775P	20010326 (60)
US 2001-278778P	20010326 (60)
US 2001-279882P	20010329 (60)
US 2001-279884P	20010329 (60)
US 2001-280147P	20010330 (60)
US 2001-283083P	20010411 (60)
US 2001-282992P	20010411 (60)
US 2001-285133P	20010420 (60)
US 2001-285749P	20010423 (60)
US 2001-288327P	20010503 (60)
US 2001-288504P	20010503 (60)
US 2001-294047P	20010529 (60)
US 2001-294473P	20010530 (60)
US 2001-296964P	20010608 (60)
US 2001-298959P	20010618 (60)
US 2001-299324P	20010619 (60)
US 2001-312020P	20010813 (60)
US 2001-312908P	20010816 (60)
US 2001-312889P	20010816 (60)
US 2001-313930P	20010821 (60)
US 2001-315470P	20010828 (60)
US 2001-316447P	20010831 (60)
US 2001-318115P	20010907 (60)
US 2001-318118P	20010907 (60)
US 2001-318740P	20010912 (60)
US 2001-323379P	20010919 (60)
US 2001-330308P	20011018 (60)
US 2001-330245P	20011018 (60)
US 2001-332701P	20011114 (60)
US 2001-271664P	20010226 (60)

DOCUMENT TYPE: Utility
 FILE SEGMENT: APPLICATION
 LEGAL REPRESENTATIVE: Ivor R. Elrifi, Ph.D.,
 Mintz, Levin, Cohn, Ferris,
 Glovsky and Popeo, P.C., One Financial
 Center, Boston,
 MA, 02111

NUMBER OF CLAIMS: 49
 EXEMPLARY CLAIM: 1
 LINE COUNT: 59681
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB Disclosed herein are nucleic acid sequences that
 encode novel
 polypeptides. Also disclosed are polypeptides
 encoded by these nucleic
 acid sequences, and antibodies, which
 immunospecifically-bind to the
 polypeptide, as well as derivatives, variants,
 mutants, or fragments of
 the aforementioned polypeptide, polynucleotide, or
 antibody. The
 invention further discloses therapeutic, diagnostic
 and research methods
 for diagnosis, treatment, and prevention of
 disorders involving any one
 of these novel human nucleic acids and proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 9 OF 68 USPATFULL on STN
 ACCESSION NUMBER: 2004:31217 USPATFULL
 TITLE: Wise/Sost nucleic acid sequences
 and amino acid
 sequences

INVENTOR(S): Krumlauf, Robb, Mission Hills,
 KS, UNITED STATES
 Ellies, Debra, Kansas City, MO, UNITED
 STATES

NUMBER	KIND	DATE
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PATENT INFORMATION: US 2004023356 A1
 20040205
 APPLICATION INFO.: US 2003-464368 A1
 20030616 (10)

NUMBER	DATE
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PRIORITY INFORMATION: US 2002-388970P
 20020614 (60)
 DOCUMENT TYPE: Utility
 FILE SEGMENT: APPLICATION
 LEGAL REPRESENTATIVE: POLSINELLI SHALTON
 & WELTE, P.C., Suite 1000, 700 W.
 47th Street, Kansas City, MO, 64108
 NUMBER OF CLAIMS: 235
 EXEMPLARY CLAIM: 1
 NUMBER OF DRAWINGS: 18 Drawing Page(s)
 LINE COUNT: 4672
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The present invention relates to nucleic acid
 sequences and amino acid
 sequences which influence bone deposition, the
 Wnt pathway, ocular
 development, tooth development, and may bind to
 LRP. The nucleic acid
 sequence and polypeptides include Wise and Sost
 as well as a family of
 molecules which express a cysteine knot
 polypeptide. Additionally, the
 present invention relates to various molecular tools
 derived from the
 nucleic acids and polypeptides including vectors,
 transfected host
 cells, monoclonal antibodies, Fab fragments, and
 methods for impacting
 the pathways.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 10 OF 68 USPATFULL on STN
 ACCESSION NUMBER: 2004:18907 USPATFULL
 TITLE: Compositions and methods for
 modulating cell

differentiation
 INVENTOR(S): Lassar, Andrew B., Newton
 Center, MA, UNITED STATES
 Mercola, Mark, Del Mar, CA, UNITED
 STATES

Gupta, Ruchika, San Diego, CA,
 UNITED STATES
 Marvin, Martha, Brookline, MA, UNITED
 STATES

Schneider, Valerie, Philadelphia, PA,
 UNITED STATES
 Tzahor, Eldad, Brookline, MA, UNITED
 STATES

Brott, Barbara, Boston, MA, UNITED
 STATES

Sokol, Sergei, Boston, MA, UNITED
 STATES

NUMBER	KIND	DATE
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PATENT INFORMATION: US 2004014209 A1
20040122
APPLICATION INFO.: US 2003-351275 A1
20030123 (10)

NUMBER DATE

PRIORITY INFORMATION: US 2002-351126P
20020123 (60)

US 2002-352456P 20020128 (60)

US 2002-352665P 20020129 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: FOLEY HOAG, LLP,
PATENT GROUP, WORLD TRADE CENTER WEST,
155 SEAPORT BLVD, BOSTON, MA,

02110

NUMBER OF CLAIMS: 61

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 24 Drawing Page(s)

LINE COUNT: 4008

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to compositions and methods for stimulating differentiation of stem cells into cardiac cells. The methods of the invention involve contacting a population cells comprising stem cells with at least one Wnt antagonist, such as a polypeptide or polypeptide fragment. In certain embodiments, the methods of the invention involve ***Dkk*** ***proteins*** or fragments, homologs, derivatives, variants, or peptidomimetics thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 11 OF 68 USPATFULL on STN
ACCESSION NUMBER: 2004:13003 USPATFULL
TITLE: Diagnosis, prognosis and
identification of potential
therapeutic targets of multiple myeloma
based on gene

expression profiling

INVENTOR(S): Shaughnessy, John D., Little
Rock, AR, UNITED STATES

Zhan, Fenghuang, Little Rock, AR,

UNITED STATES

Barlogie, Bart, Little Rock, AR, UNITED

STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2004009523 A1
20040115

APPLICATION INFO.: US 2003-454263 A1
20030604 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser.
No. US 2003-409004, filed
on 8 Apr 2003, PENDING Continuation-
in-part of Ser. No.

US 2002-289746, filed on 7 Nov 2002,

PENDING

NUMBER DATE

PRIORITY INFORMATION: US 2002-403075P
20020813 (60)

US 2001-348238P 20011107 (60)

US 2002-355386P 20020208 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Benjamin Aaron Adler,
ADLER & ASSOCIATES, 8011 Candle
Lane, Houston, TX, 77071

NUMBER OF CLAIMS: 26

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 24 Drawing Page(s)

LINE COUNT: 4510

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Gene expression profiling between normal B cells/plasma cells and multiple myeloma cells revealed four distinct subgroups of multiple myeloma plasma cells that have significant correlation with clinical characteristics known to be associated with poor prognosis. Diagnosis for multiple myeloma (and possibly monoclonal gammopathy of undetermined significance) based on differential expression of 14 genes, as well as prognostics for the four subgroups of multiple myeloma based on the expression of 24 genes were also established. Gene expression profiling also allows placing multiple myeloma into a developmental schema parallel to that of normal plasma cell differentiation. The development of a gene expression- or developmental stage-based classification system for multiple myeloma would lead to rational design of more accurate and sensitive diagnostics, prognostics and tumor-specific therapies for multiple myeloma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 12 OF 68 EMBASE COPYRIGHT 2005
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on STN

ACCESSION NUMBER: 2004243930 EMBASE

TITLE: Multiple mechanisms for Wnt11-
mediated repression of the

canonical Wnt signaling pathway.

AUTHOR: Maye P.; Zheng J.; Li L.; Wu D.

CORPORATE SOURCE: D. Wu, Dept. of Genet. and
Devmtl. Biology, Univ. of
Connecticut Health Center, MC3301, 263
Farmington Ave.,
Farmington, CT 06030, United States.

dwu@neuron.uchc.edu

SOURCE: Journal of Biological Chemistry, (4
Jun 2004) 279/23

(24659-24665).

Refs: 48

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The effect of a noncanonical Wnt, Wnt11, on
canonical Wnt signaling

stimulated by Wnt1 and activated forms of

LRP5 (low density

lipoprotein receptor-related protein-5), Dishevelled1 (Dvl1), and .beta.-catenin was examined in NIH3T3 cells and P19 embryonic carcinoma cells. Wnt11 repressed Wnt1-mediated activation of LEF-1 reporter activity in both cell lines. However, Wnt11 was unable to inhibit canonical signaling activated by ***LRP5***, Dvl1, or .beta.-catenin in NIH3T3 cells, although it could in P19 cells. In addition, Wnt11-mediated inhibition of canonical signaling in NIH3T3 cells is ligand-specific; Wnt11 could effectively repress canonical signaling activated by Wnt1, Wnt3, or Wnt3a but not by Wnt7a or Wnt7b. Co-culture experiments with NIH3T3 cells showed that the co-expression of Wnt11 with Wnt1 was not an essential requirement for the inhibition, suggesting receptor competition as a possible mechanism. Moreover, in both cell types, elevation of intracellular Ca(2+) levels, which can result from Wnt11 treatment, led to the inhibition of canonical signaling. This result suggests that Wnt11 might not be able to signal in NIH3T3. Furthermore, P19 cells were found to express both endogenous canonical Wnts and Wnt11. Knockdown of Wnt11 expression using siRNA resulted in increased LEF-1 reporter activity, thus indicating that Wnt11-mediated suppression of canonical signaling exists in vivo.

L7 ANSWER 13 OF 68 MEDLINE on STN
 DUPLICATE 2
 ACCESSION NUMBER: 2004197066 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 14739301
 TITLE: The low density lipoprotein receptor-1, LRP1, interacts with the human frizzled-1 (HFz1) and down-regulates the canonical Wnt signaling pathway.
 AUTHOR: Zilberberg Alona; Yaniv Abraham; Gazit Arnona
 CORPORATE SOURCE: Department of Human Microbiology, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel.
 SOURCE: Journal of biological chemistry, (2004 Apr 23) 279 (17) 17535-42.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200406
 ENTRY DATE: Entered STN: 20040420
 Last Updated on STN: 20040611
 Entered Medline: 20040610
 AB Members of the low density lipoprotein receptor family (LDLR),

LRP5 /6, were shown to interact with the Frizzled (Fz) receptors and to function as Wnt coreceptors. Here we show that mLRP4T100, a minireceptor of LRP1, another member of the LDLR family, interacts with the human Fz-1 (HFz1), previously shown to serve as a receptor transmitting the canonical Wnt-3a-induced signaling cascade. However, in contrast to ***LRP5*** /6, mLRP4T100, as well as the full-length LRP1, did not cooperate with HFz1 in transmitting the Wnt-3a signaling but rather repressed it. mLRP4T100 inhibitory effect was displayed also by endocytosis-defective mLRP4T100 mutants, suggesting that LRP1 repressive effect is not attributable to LRP1-mediated enhanced HFz1 internalization and subsequent degradation. Enforced expression of mLRP4T100 decreased the capacity of HFz1 cysteine-rich domain (CRD) to interact with LRP6, in contrast to HFz1-CRD/Wnt-3a interaction that was not disrupted by overexpressing mLRP4T100. These data suggest that LRP1, by sequestering HFz1, disrupts the receptor/coreceptor complex formation, leading to the repression of the canonical Wnt signaling. Thus, this study implies that the ability to interact with Fz receptors is shared by several members of the LDLR family. However, whereas some members of the LDLR family, such as ***LRP5*** /6, interact with Fz and serve as Wnt coreceptors, others negatively regulate Wnt signaling, presumably by sequestering Fz.

L7 ANSWER 14 OF 68 MEDLINE on STN
 DUPLICATE 3
 ACCESSION NUMBER: 2004562796 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15459103
 TITLE: Wnt signals across the plasma membrane to activate the beta-catenin pathway by forming oligomers containing its receptors, Frizzled and LRP.
 AUTHOR: Cong Feng; Schweizer Liang; Varmus Harold
 CORPORATE SOURCE: Cancer Biology and Genetics Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA..
 feng.cong@pharma.novartis.com
 SOURCE: Development (Cambridge, England), (2004 Oct) 131 (20) 5103-15.
 Journal code: 8701744. ISSN: 0950-1991.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200412
 ENTRY DATE: Entered STN: 20041111
 Last Updated on STN: 20041229

Entered Medline: 20041228

AB Wnt-induced signaling via beta-catenin plays crucial roles in animal development and tumorigenesis. Both a seven-transmembrane protein in the Frizzled family and a single transmembrane protein in the LRP family (***LDL*** - ***receptor*** - ***related*** ***protein*** ***5*** /6 or Arrow) are essential for efficiently transducing a signal from Wnt, an extracellular ligand, to an intracellular pathway that stabilizes beta-catenin by interfering with its rate of destruction. However, the molecular mechanism by which these two types of membrane receptors synergize to transmit the Wnt signal is not known. We have used mutant and chimeric forms of Frizzled, LRP and ***Wnt*** ***proteins***, small inhibitory RNAs, and assays for beta-catenin-mediated signaling and protein localization in *Drosophila* S2 cells and mammalian 293 cells to study transmission of a Wnt signal across the plasma membrane. Our findings are consistent with a mechanism by which ***Wnt*** ***protein*** binds to the extracellular domains of both LRP and Frizzled receptors, forming membrane-associated hetero-oligomers that interact with both Disheveled (via the intracellular portions of Frizzled) and Axin (via the intracellular domain of LRP). This model takes into account several observations reported here: the identification of intracellular residues of Frizzled required for beta-catenin signaling and for recruitment of Dvl to the plasma membrane; evidence that Wnt3A binds to the ectodomains of LRP and Frizzled; and demonstrations that a requirement for Wnt ligand can be abrogated by chimeric receptors that allow formation of Frizzled-LRP hetero-oligomers. In addition, the beta-catenin signaling mediated by ectopic expression of LRP is not dependent on Disheveled or Wnt, but can also be augmented by oligomerization of LRP receptors.

L7 ANSWER 15 OF 68 MEDLINE on STN
 DUPLICATE 4
 ACCESSION NUMBER: 2004306948 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15064719
 TITLE: Truncated mutants of the putative Wnt receptor LRP6/Arrow can stabilize beta-catenin independently of Frizzled proteins.
 AUTHOR: Brennan Keith; Gonzalez-Sancho Jose M; Castelo-Soccio Leslie A; Howe Louise R; Brown Anthony M C
 CORPORATE SOURCE: Strang Cancer Research Laboratory at The Rockefeller

University, 1230 York Avenue, New York, NY 10021, USA.
 CONTRACT NUMBER: CA47207 (NCI) GM67739 (NIGMS)
 SOURCE: Oncogene, (2004 Jun 17) 23 (28) 4873-84.
 Journal code: 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200407
 ENTRY DATE: Entered STN: 20040624
 Last Updated on STN: 20040717
 Entered Medline: 20040716

AB Secreted signaling proteins of the Wnt family are known to regulate a diverse range of developmental processes, and their signaling pathway through beta-catenin is frequently activated in cancer. The identification of both Frizzled and ***LRP5*** /6 (LRP: low-density lipoprotein receptor-related protein) proteins as components of cell-surface receptors for ***Wnt*** ***proteins*** has raised questions about their individual functions. We have investigated this issue through a structure-function analysis of Frizzled and LRP proteins that have been implicated in Wnt1 signaling. Consistent with other reports, we find that LRP6/Arrow proteins deleted for their extracellular domain are able to activate the Wnt/beta-catenin signaling pathway. Importantly, our results demonstrate that this signaling from LRP6/Arrow derivatives can occur in a Frizzled- and ligand-independent manner. Furthermore, we show that the PPSP motifs within the intracellular domain of LRP6 are required for signaling. In contrast to results with LRP6, overexpression of Frizzled proteins did not activate the pathway. Based on evidence of ligand binding to both Frizzled and LRP6, current models suggest that both proteins are components of a Wnt receptor complex that signals to beta-catenin. In light of these models, our data imply that ***LRP5*** /6/Arrow proteins constitute the distal signal-initiating component of these receptors. The results also support the notion that ***LRP5*** /6 are candidate oncogenes.
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L7 ANSWER 16 OF 68 MEDLINE on STN
 DUPLICATE 5
 ACCESSION NUMBER: 2004263880 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15143170
 TITLE: ***Wnt*** ***proteins*** induce dishevelled phosphorylation via an ***LRP5*** /6-independent

mechanism, irrespective of their ability to stabilize beta-catenin.

AUTHOR: Gonzalez-Sancho Jose M; Brennan Keith R; Castelo-Soccio

Leslie A; Brown Anthony M C
CORPORATE SOURCE: Strang Cancer Research Laboratory at The Rockefeller University, 1230 York Ave., New York, NY 10021, USA.

CONTRACT NUMBER: CA47207 (NCI) GM67739 (NIGMS)

SOURCE: Molecular and cellular biology, (2004 Jun) 24 (11) 4757-68.

Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200406

ENTRY DATE: Entered STN: 20040528

Last Updated on STN: 20040624

Entered Medline: 20040621

AB Wnt glycoproteins play essential roles in the development of metazoan organisms. Many ***Wnt*** ***proteins***, such as Wnt1, activate the well-conserved canonical Wnt signaling pathway, which results in accumulation of beta-catenin in the cytosol and nucleus. Other Wnts, such as Wnt5a, activate signaling mechanisms which do not involve beta-catenin and are less well characterized. Dishevelled (Dvl) is a key component of Wnt/beta-catenin signaling and becomes phosphorylated upon activation of this pathway. In addition to Wnt1, we show that several ***Wnt*** ***proteins***, including Wnt5a, trigger phosphorylation of mammalian Dvl proteins and that this occurs within 20 to 30 min. Unlike the effects of Wnt1, phosphorylation of Dvl in response to Wnt5a is not concomitant with beta-catenin stabilization, indicating that Dvl phosphorylation is not sufficient to activate canonical Wnt/beta-catenin signaling.

Moreover, neither Dickkopf1, which inhibits Wnt/beta-catenin signaling by binding the Wnt coreceptors ***LRP5*** and -6, nor dominant-negative ***LRP5*** /6 constructs could block Wnt-mediated Dvl phosphorylation.

We conclude that Wnt-induced phosphorylation of Dvl is independent of

LRP5 /6 receptors and that canonical Wnts can elicit both

LRP-dependent (to beta-catenin) and LRP-independent (to Dvl) signals. Our data also present Dvl phosphorylation as a general biochemical assay for

Wnt ***protein*** function, including those Wnts that do not activate the Wnt/beta-catenin pathway.

L7 ANSWER 17 OF 68 MEDLINE on STN
DUPLICATE 6

ACCESSION NUMBER: 2004244690 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15143163

TITLE: The ***LRP5*** high-bone-mass G171V mutation disrupts

LRP5 interaction with Mesd.

AUTHOR: Zhang Yazhou; Wang Yang; Li Xiaofeng; Zhang Jianhong; Mao

Junhao; Li Zhong; Zheng Jie; Li Lin; Harris Steve; Wu

Dianqing

CORPORATE SOURCE: Department of Genetics and Developmental Biology, University of Connecticut Health Center, 263 Farmington

Ave., Farmington, CT 06410, USA.

CONTRACT NUMBER: CA85420 (NCI)

GM54167 (NIGMS)

SOURCE: Molecular and cellular biology, (2004 Jun) 24 (11) 4677-84.

Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200406

ENTRY DATE: Entered STN: 20040515

Last Updated on STN: 20040624

Entered Medline: 20040621

AB The mechanism by which the high-bone-mass (HBM) mutation (G171V) of the Wnt coreceptor ***LRP5*** regulates canonical Wnt signaling was investigated. The mutation was previously shown to reduce DKK1-mediated antagonism, suggesting that the first YWTD repeat domain where G171 is located may be responsible for DKK-mediated antagonism. However, we found that the third YWTD repeat, but not the first repeat domain, is required for DKK1-mediated antagonism. Instead, we found that the G171V mutation disrupted the interaction of ***LRP5*** with Mesd, a chaperone protein for ***LRP5*** /6 that is required for transport of the coreceptors to cell surfaces, resulting in fewer ***LRP5*** molecules on the cell surface. Although the reduction in the number of cell surface ***LRP5*** molecules led to a reduction in Wnt signaling in a paracrine paradigm, the mutation did not appear to affect the activity of coexpressed Wnt in an autocrine paradigm. Together with the observation that osteoblast cells produce autocrine canonical Wnt, Wnt7b, and that osteocytes produce paracrine DKK1, we think that the G171V mutation may cause an increase in Wnt activity in osteoblasts by reducing the number of targets for paracrine DKK1 to antagonize without affecting the activity of autocrine Wnt.

L7 ANSWER 18 OF 68 MEDLINE on STN
DUPLICATE 7

ACCESSION NUMBER: 2004270551 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15142971
TITLE: The Wnt co-receptors ***Lrp5*** and Lrp6 are essential

for gastrulation in mice.

AUTHOR: Kelly Olivia G; Pinson Kathy I;
Skames William C

CORPORATE SOURCE: Department of Molecular
and Cell Biology, University of

California at Berkeley, Berkeley, CA

94720-3200, USA.

SOURCE: Development (Cambridge, England),
(2004 Jun) 131 (12)

2803-15.

Journal code: 8701744. ISSN: 0950-1991.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200408

ENTRY DATE: Entered STN: 20040602

Last Updated on STN: 20040811

Entered Medline: 20040810

AB Recent work has identified LDL receptor-related
family members,

Lrp5 and Lrp6, as co-receptors for the
transduction of Wnt
signals. Our analysis of mice carrying mutations in
both ***Lrp5***

and Lrp6 demonstrates that the functions of these
genes are redundant and
are essential for gastrulation. ***Lrp5*** ;Lrp6
double homozygous

mutants fail to establish a primitive streak, although
the anterior
visceral endoderm and anterior epiblast fates are
specified. Thus,

Lrp5 and Lrp6 are required for posterior
patterning of the
epiblast, consistent with a role in transducing Wnt
signals in the early

embryo. Interestingly, ***Lrp5*** (+/-);Lrp6(-/-)
embryos die shortly

after gastrulation and exhibit an accumulation of
cells at the primitive

streak and a selective loss of paraxial mesoderm. A
similar phenotype is

observed in Fgf8 and Fgfr1 mutant embryos and
provides genetic evidence in

support of a molecular link between the Fgf and Wnt
signaling pathways in

patterning nascent mesoderm. ***Lrp5*** (+/-

);Lrp6(-/-) embryos also

display an expansion of anterior primitive streak
derivatives and anterior

neurectoderm that correlates with increased Nodal
expression in these

embryos. The effect of reducing, but not eliminating,
Wnt signaling in

Lrp5 (+/-);Lrp6(-/-) mutant embryos provides
important insight into

the interplay between Wnt, Fgf and Nodal signals in
patterning the early
mouse embryo.

L7 ANSWER 19 OF 68 MEDLINE on STN

DUPLICATE 8

ACCESSION NUMBER: 2004190880 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15087387

TITLE: Dickkopf 3 inhibits invasion and motility
of Saos-2

osteosarcoma cells by modulating the Wnt-
beta-catenin

pathway.

AUTHOR: Hoang Bang H; Kubo Tadahiko;

Healey John H; Yang Rui;

Nathan Saminathan S; Kolb E Anders;

Mazza BethAnne; Meyers

Paul A; Gorlick Richard

CORPORATE SOURCE: Department of Surgery,
Orthopaedic Surgery Service,

Memorial Sloan-Kettering Cancer Center,

New York, New York,

USA.

CONTRACT NUMBER: CA-81832 (NCI)

SOURCE: Cancer research, (2004 Apr 15) 64
(8) 2734-9.

Journal code: 2984705R. ISSN: 0008-

5472.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200406

ENTRY DATE: Entered STN: 20040417

Last Updated on STN: 20040611

Entered Medline: 20040610

AB Osteosarcoma (OS) is a primary malignancy of
bone with a tendency to

metastasize early. Despite intensive chemotherapy
and surgical resection,

approximately 30% of patients still develop distant
metastasis. Our

previous work using clinical OS samples suggested
that expression of the

Wnt receptor ***LRP5*** might be associated with
tumor metastasis. In

the present study, we used a Dickkopf (Dkk) family
member and a

dominant-negative ***LRP5*** receptor construct
to modulate Wnt

signaling in OS cells. Saos-2 cells, which ectopically
express Dkk-3, do

not undergo apoptosis and exhibit enhanced
resistance to serum starvation

and chemotherapy-induced cytotoxicity.

Transfection of Dkk-3 and

dominant-negative ***LRP5*** into Saos-2 cells
significantly reduces

invasion capacity and cell motility. This blockade is
associated with

changes in cell morphology consistent with a less
invasive phenotype. In

addition, Dkk-3 and dominant-negative ***LRP5***
also induce changes

in beta-catenin localization consistent with an
increase in cell-cell

adhesion. Taken together, these results support a
possible role for Wnt

signaling in the pathobiology and progression of
human OS.

L7 ANSWER 20 OF 68 EMBASE COPYRIGHT 2005
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on STN

ACCESSION NUMBER: 2004288152 EMBASE

TITLE: Hypomorphic expression of Dkk1 in the
doublebridge mouse:

Dose dependence and compensatory interactions with Lrp6.
AUTHOR: MacDonald B.T.; Adamska M.; Meisler M.H.
CORPORATE SOURCE: M.H. Meisler, Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109-0618, United States.
meislerm@umich.edu
SOURCE: Development, (2004) 131/11 (2543-2552).

Refs: 48
ISSN: 0950-1991 CODEN: DEVPED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology

022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB doubleridge is a transgene-induced mouse mutation displaying forelimb postaxial polysyndactyly. We have cloned the doubleridge transgene insertion site and demonstrate that doubleridge acts in cis from a distance of 150 kb to reduce the expression of dickkopf 1 (Dkk1), the secreted Wnt antagonist. Expression of Dkk1 from the doubleridge allele ranges from 35% of wild-type level in E7.0 head to <1% of wild type in E13.5 tail. doubleridge homozygotes and doubleridge/null compound heterozygotes are viable. An allelic series combining the wild-type, doubleridge and null alleles of Dkk1 demonstrates the effect of varying Dkk1 concentration on development of limb, head and vertebrae. Decreasing expression of Dkk1 results in hemivertebral fusions in progressively more anterior positions, with severity increasing from tail kinks to spinal curvature. We demonstrated interaction between Dkk1 and the Wnt co-receptors ***Lrp5*** and Lrp6 by analysis of several types of double mutants. The polydactyly of Dkk1(d/d) mice was corrected by reduced expression of ***Lrp5*** or Lrp6. The posterior digit loss and axial truncation characteristic of Lrp6 null mice was partially corrected by reduction of Dkk1. Similarly, the anterior head truncation characteristic of Dkk1 null mice was rescued by reduction of Lrp6. These compensatory interactions between Dkk1 and Lrp6 demonstrate the importance of correctly balancing positive and negative regulation of Wnt signaling during mammalian development.

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on STN
ACCESSION NUMBER: 2004204271 EMBASE

TITLE: High-Bone-Mass Disease and ***LRP5*** [2] (multiple letters).
AUTHOR: Whyte M.P.; Reinus W.H.; Mumm S.; Boyden L.M.; Insogna K.; Lifton R.P.
CORPORATE SOURCE: Dr. M.P. Whyte, Washington Univ. School of Medicine, St. Louis, MO 63110, United States
SOURCE: New England Journal of Medicine, (13 May 2004) 350/20

(2096-2099).
ISSN: 0028-4793 CODEN: NEJMAG
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 005 General Pathology and Pathological Anatomy

022 Human Genetics
029 Clinical Biochemistry
033 Orthopedic Surgery
LANGUAGE: English

L7 ANSWER 22 OF 68 MEDLINE on STN
DUPLICATE 9
ACCESSION NUMBER: 2004225645 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15084453
TITLE: ***LDL*** ***receptor*** -
related
proteins ***5*** and 6 in Wnt/beta-catenin signaling: arrows point the way.
AUTHOR: He Xi; Semenov Mikhail; Tamai Keiko; Zeng Xin
CORPORATE SOURCE: Division of Neuroscience, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA..
xi.he@childrens.harvard.edu
SOURCE: Development (Cambridge, England), (2004 Apr) 131 (8)
1663-77. Ref: 142
Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040506
Last Updated on STN: 20040604
Entered Medline: 20040603
AB Wnt signaling through the canonical beta-catenin pathway plays essential roles in development and disease. Low-density-lipoprotein receptor-related proteins 5 and 6 (***Lrp5*** and Lrp6) in vertebrates, and their Drosophila ortholog Arrow, are single-span transmembrane proteins that are indispensable for Wnt/beta-catenin signaling, and are likely to act as Wnt co-receptors. This review highlights recent progress and unresolved issues in understanding the function and regulation of Arrow/ ***Lrp5*** /Lrp6 in Wnt signaling. We discuss Arrow/ ***Lrp5*** /Lrp6 interactions with Wnt and the Frizzled

family of Wnt receptors, and with the intracellular beta-catenin degradation apparatus. We also discuss the regulation of ***Lrp5*** /Lrp6 by other extracellular ligands, and ***LRP5*** mutations associated with familial osteoporosis and other disorders.

L7 ANSWER 23 OF 68 MEDLINE on STN
ACCESSION NUMBER: 2004143155 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15035989
TITLE: Vascular development in the retina and inner ear: control by Norrin and Frizzled-4, a high-affinity ligand-receptor pair.
AUTHOR: Xu Qiang; Wang Yanshu; Dabdoub Alain; Smallwood Philip M; Williams John; Woods Chad; Kelley Matthew W; Jiang Li; Tasman William; Zhang Kang; Nathans Jeremy
CORPORATE SOURCE: Department of Molecular Biology and Genetics, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
SOURCE: Cell, (2004 Mar 19) 116 (6) 883-95. Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040324 Last Updated on STN: 20040428 Entered Medline: 20040427
AB Incomplete retinal vascularization occurs in both Norrie disease and familial exudative vitreoretinopathy (FEVR). Norrin, the protein product of the Norrie disease gene, is a secreted protein of unknown biochemical function. One form of FEVR is caused by defects in Frizzled-4 (Fz4), a presumptive Wnt receptor. We show here that Norrin and Fz4 function as a ligand-receptor pair based on (1) the similarity in vascular phenotypes caused by Norrin and Fz4 mutations in humans and mice, (2) the specificity and high affinity of Norrin-Fz4 binding, (3) the high efficiency with which Norrin induces Fz4- and Lrp-dependent activation of the classical Wnt pathway, and (4) the signaling defects displayed by disease-associated variants of Norrin and Fz4. These data define a Norrin-Fz4 signaling system that plays a central role in vascular development in the eye and ear, and they indicate that ligands unrelated to Wnts can act through Fz receptors.

L7 ANSWER 24 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2004148103 EMBASE
TITLE: Mutations in ***LRP5*** or FZD4 Underlie the Common Familial Exudative Vitreoretinopathy Locus on Chromosome 11q.
AUTHOR: Toomes C.; Bottomley H.M.; Jackson R.M.; Towns K.V.; Scott S.; Mackey D.A.; Craig J.E.; Jiang L.; Yang Z.; Trembath R.; Woodruff G.; Gregory-Evans C.Y.; Gregory-Evans K.; Parker M.J.; Black G.C.M.; Downey L.M.; Zhang K.; Inglehearn C.F.
CORPORATE SOURCE: Dr. C. Toomes, Molecular Medicine Unit, Clinical Sciences Building, St. James's University Hospital, Leeds LS9 7TF, United Kingdom. c.toomes@leeds.ac.uk
SOURCE: American Journal of Human Genetics, (2004) 74/4 (721-730). Refs: 48
ISSN: 0002-9297 CODEN: AJHGAG
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology 022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Familial exudative vitreoretinopathy (FEVR) is an inherited blinding disorder of the retinal vascular system. Autosomal dominant FEVR is genetically heterogeneous, but its principal locus, EVR1, is on chromosome 11q13-q23. The gene encoding the Wnt receptor frizzled-4 (FZD4) was recently reported to be the EVR1 gene, but our mutation screen revealed fewer patients harboring mutations than expected. Here, we describe mutations in a second gene at the EVR1 locus, low-density-lipoprotein receptor-related protein 5 (***LRP5***), a Wnt coreceptor. This finding further underlines the significance of Wnt signaling in the vascularization of the eye and highlights the potential dangers of using multiple families to refine genetic intervals in gene-identification studies.

L7 ANSWER 25 OF 68 MEDLINE on STN
DUPLICATE 10
ACCESSION NUMBER: 2004605612 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15578921
TITLE: Wnt/beta-catenin signaling pathway as a novel cancer drug target.
AUTHOR: Luu Hue H; Zhang Ruiwen; Haydon Rex C; Rayburn Elizabeth; Kang Quan; Si Wei; Park Jong Kyung; Wang Hui; Peng Ying; Jiang Wei; He Tong-Chuan
CORPORATE SOURCE: Molecular Oncology Laboratory, Department of Surgery, The University of Chicago Medical Center, Chicago, IL 60637,

USA.
 SOURCE: Current cancer drug targets, (2004 Dec) 4 (8) 653-71. Ref: 291
 Journal code: 101094211. ISSN: 1568-0096.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200502
 ENTRY DATE: Entered STN: 20041207
 Last Updated on STN: 20050211
 Entered Medline: 20050210
 AB ***Wnt*** ***proteins*** are a large family of secreted glycoproteins. ***Wnt*** ***proteins*** bind to the Frizzled receptors and ***LRP5*** /6 co-receptors, and through stabilizing the critical mediator beta-catenin, initiate a complex signaling cascade that plays an important role in regulating cell proliferation and differentiation. Deregulation of the canonical Wnt/beta-catenin signaling pathway, mostly by inactivating mutations of the APC tumor suppressor, or oncogenic mutations of beta-catenin, has been implicated in colorectal tumorigenesis. Although oncogenic mutations of beta-catenin have only been discovered in a small fraction of non-colon cancers, elevated levels of beta-catenin protein, a hallmark of activated canonical Wnt pathway, have been observed in most common forms of human malignancies, indicating that activation of this pathway may play an important role in tumor development. Over the past 15 years, our understanding of this signaling pathway has significantly improved with the identification of key regulatory proteins and the important downstream targets of beta-catenin/Tcf transactivation complex. Given the fact that Wnt/beta-catenin signaling is tightly regulated at multiple cellular levels, the pathway itself offers ample targeting nodal points for cancer drug development. In this review, we discuss some of the strategies that are being used or can be explored to target key components of the Wnt/beta-catenin signaling pathway in rational cancer drug discovery.

L7 ANSWER 26 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2005024652 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15651377
 TITLE: Wnt coreceptor low density lipoprotein receptor related protein 5 (***LRP5***) mediates the bone formation and glucose induced insulin secretion.
 AUTHOR: Sakai Juro

SOURCE: Nippon Ronen Igakkai zasshi. Japanese journal of geriatrics, (2004 Nov) 41 (6) 625-8.
 Journal code: 7507332. ISSN: 0300-9173.
 PUB. COUNTRY: Japan
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: Japanese
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200502
 ENTRY DATE: Entered STN: 20050118
 Last Updated on STN: 20050202
 Entered Medline: 20050201

L7 ANSWER 27 OF 68 MEDLINE on STN
 DUPLICATE 11
 ACCESSION NUMBER: 2004148705 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15040835
 TITLE: Cooperation between TGF-beta and Wnt pathways during chondrocyte and adipocyte differentiation of human marrow stromal cells.
 AUTHOR: Zhou Shuanhu; Eid Karim; Glowacki Julie
 CORPORATE SOURCE: Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
 SOURCE: Journal of bone and mineral research : official journal of the American Society for Bone and Mineral Research, (2004 Mar) 19 (3) 463-70.
 Journal code: 8610640. ISSN: 0884-0431.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200411
 ENTRY DATE: Entered STN: 20040326
 Last Updated on STN: 20041219
 Entered Medline: 20041119
 AB Human marrow stromal cells have the potential to differentiate to chondrocytes or adipocytes. We show interactions between TGF-beta and Wnt signaling pathways during stimulation of chondrogenesis and inhibition of adipogenesis. Combining these signals may be useful in marrow stromal cell therapies. INTRODUCTION: Human bone marrow stromal cells (hMSCs) have the potential to differentiate to lineages of mesenchymal tissues, including cartilage, fat, bone, tendon, and muscle. Agents like transforming growth factor (TGF)-beta promote chondrocyte differentiation at the expense of adipocyte differentiation. In other processes, TGF-beta and Wnt/wingless signaling pathways play major roles in controlling certain developmental events and activation of specific target genes. We tested whether these pathways interact during differentiation of chondrocytes and

adipocytes in human marrow stromal cells.

MATERIALS AND METHODS: Both a line of human marrow stromal cells (KM101) and freshly isolated hMSCs were studied. Reverse transcriptase-polymerase chain reaction (RT-PCR), Western blot, and macroarrays were used for analysis of the modulation of TGF-beta1 on Wnt signaling-associated genes, chondrocyte differentiation genes, and TGFbeta/bone morphogenetic protein (BMP) signaling-associated genes in KM101 cells. Early passage hMSCs obtained from 42- and 58-year-old women were used for the effects of TGF-beta and/or Wnt (mimicked by LiCl) signals on chondrocyte and adipocyte differentiation in two-dimensional (2-D) cultures, 3-D pellet cultures, and collagen sponges.

RESULTS: As indicated by macroarray, RT-PCR, and Western blot, TGF-beta activated genes in the TGF-beta/Smad pathway, upregulated Wnt2, Wnt4, Wnt5a, Wnt7a, Wnt10a, and Wnt co-receptor ***LRP5***, and increased nuclear accumulation and stability of beta-catenin in KM101 cells.

TGF-beta upregulated chondrocyte gene expression in KM101 cells and also stimulated chondrocyte differentiation and inhibited adipocyte differentiation in hMSCs, synergistically with Wnt signal. Finally, hMSCs cultured in 3-D collagen sponges were stimulated by TGF-beta1 to express aggrecan and collagen type II mRNA, whereas expression of lipoprotein lipase was inhibited.

CONCLUSIONS: In summary, TGF-beta stimulated chondrocyte differentiation and inhibited adipocyte differentiation of hMSCs in vitro. The activation of both TGF-beta and Wnt signal pathways by TGF-beta, and synergy between TGF-beta and Wnt signals, supports the view that Wnt-mediated signaling is one of the mechanisms of TGF-beta's effects on chondrocyte and adipocyte differentiation of hMSCs.

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ACCESSION NUMBER: 2004267144 EMBASE
TITLE: Genetic determinants of bone mass.
AUTHOR: Baldock P.A.; Eisman J.A.
CORPORATE SOURCE: J.A. Eisman, Bone and Mineral Research Program, Garvan
Institute of Medical Research, University of New South
Wales, 384 Victoria Street, Sydney, NSW
2010, Australia.
j.eisman@garvan.org.au
SOURCE: Current Opinion in Rheumatology,
(2004) 16/4 (450-456).
Refs: 73
ISSN: 1040-8711 CODEN: CORHES
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 022 Human Genetics
031 Arthritis and Rheumatism
033 Orthopedic Surgery
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Purpose of review: This review examines recent advances in the analysis of genetic determinants of bone mass. It addresses both human and animal linkage studies as well as genetic manipulations in animals, inbred mouse models, and candidate gene analyses. Recent findings: Recent studies have implicated novel regulatory pathways in bone biology including both the neuroendocrine system and metabolic pathways linked to lipid metabolism.

Variations in the lipoprotein receptor-related protein 5 (***LRP5***), part of the Wnt-frizzled pathway, were independently identified by linkage in high and low bone mass families. Subsequently, other high bone mass syndromes have been shown to have mutations in this gene. Neural studies have shown the skeletal regulatory activity of leptin and neuropeptide Y receptors via the hypothalamus. Subsequently, the .beta.-adrenergic pathway has been implicated, with important changes in bone mass. The lipoxygenase 12/15 pathway, identified through inbred mouse models and through pharmacologic studies with specific inhibitors, has also been shown to have important effects on bone mass. These studies exemplify the value of genetic models both to identify and then confirm pathways by mutational study and pharmacologic interventions. Continuing candidate gene studies often performed with multiple loci complement such discoveries. However, these studies have not focused on the clinical endpoint of fracture and few have included large enough groups to engender confidence in the associations reported, as such studies may require thousands of individuals. Interestingly, results often differ by ethnicity, age, or gender. A small proportion have examined whether relevant genes influence response to treatment.

Summary: The combinations of human and animal genetic linkage studies have advanced understanding of the regulation of bone mass. Studies ranging from linkage to pharmacology provide optimism for new targets and treatments for osteoporosis.

.COPYRGT. 2004 Lippincott Williams & Wilkins.

L7 ANSWER 29 OF 68 MEDLINE on STN
ACCESSION NUMBER: 2004283249 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15182694
TITLE: Wnt signaling: Ig-norin the dogma.
AUTHOR: Clevers Hans

CORPORATE SOURCE: Hubrecht Laboratory,
Uppsalaalan 8, 3584 CT Utrecht, The
Netherlands.. clevers@niob.knaw.nl
SOURCE: Current biology : CB, (2004 Jun 8) 14
(11) R436-7. Ref: 11

Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040609
Last Updated on STN: 20040903
Entered Medline: 20040902

AB Secreted ***Wnt*** ***proteins*** trigger the
intracellular Wnt
signaling cascade upon engagement of dedicated
Frizzled-Lrp receptor
complexes. Unexpectedly, a non-Wnt ligand for this
receptor complex has
now been discovered. This novel ligand, Norrin, is
mutated in the
hereditary ocular Norrie syndrome.
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on STN

ACCESSION NUMBER: 2004184668 EMBASE
TITLE: Glucocorticoid enhances the expression
of dickkopf-1 in

human osteoblasts: Novel mechanism of
glucocorticoid-
induced osteoporosis.

AUTHOR: Ohnaka K.; Taniguchi H.; Kawate H.;
Nawata H.; Takayanagi
R.

CORPORATE SOURCE: K. Ohnaka, Department of
Geriatric Medicine, Graduate
School of Medical Sciences, Kyushu
University, 3-1-1
Maidashi, Higashi-ku, Fukuoka 812-8582,
Japan.

oonaka@geriat.med.kyushu-u.ac.jp
SOURCE: Biochemical and Biophysical
Research Communications, (21
May 2004) 318/1 (259-264).

Refs: 28
ISSN: 0006-291X CODEN: BBRCA
PUBLISHER IDENT.: S 0006-291X(04)00733-8

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
033 Orthopedic Surgery
037 Drug Literature Index
052 Toxicology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB To clarify the underlying mechanism of
glucocorticoid-induced
osteoporosis, we investigated the effect of
glucocorticoid on the
expression of dickkopf-1 (Dkk-1), an antagonist of
Wnt signaling, in
primary cultured human osteoblasts.
Dexamethasone markedly induced the

expression of mRNA for Dkk-1 in a dose- and time-
dependent manner. The
expression of Kremen1, a receptor for Dkk, did not
change by the treatment
with dexamethasone, while that of low-density
lipoprotein receptor-related
protein 5 (***LRP5***), a Wnt coreceptor, slightly
decreased by the
treatment with dexamethasone. Dexamethasone
increased the transcriptional
activity of the Dkk-1 gene promoter in human
osteoblasts. Serial deletion
and mutation analyses of the Dkk-1 promoter
showed that one putative
glucocorticoid responsive element-like sequence
located from -788 to
-774bp is essential for the enhancement of the Dkk-
1 promoter activity by
dexamethasone in human osteoblasts. Since the
Wnt signal is now recognized
as a crucial regulator for bone formation, the Dkk-1
enhanced by
glucocorticoid may inhibit the Wnt signal in
osteoblasts, which may be
involved in the pathogenesis of glucocorticoid-
induced osteoporosis.
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L7 ANSWER 31 OF 68 MEDLINE on STN
DUPLICATE 12
ACCESSION NUMBER: 2004032104 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14731402
TITLE: A mechanism for Wnt coreceptor
activation.

AUTHOR: Tamai Keiko; Zeng Xin; Liu
Chunming; Zhang Xinjun; Harada
Yuko; Chang Zhijie; He Xi
CORPORATE SOURCE: Division of Neuroscience,
Children's Hospital, Department
of Neurology, Harvard Medical School,
Boston, MA 02115,
USA.

SOURCE: Molecular cell, (2004 Jan 16) 13 (1)
149-56.
Journal code: 9802571. ISSN: 1097-2765.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20040121
Last Updated on STN: 20040310
Entered Medline: 20040309

AB ***LDL*** ***receptor*** ***related***
proteins
5 and 6 (***LRP5*** /6) and their
Drosophila homolog Arrow are
single-span transmembrane proteins essential for
Wnt/beta-catenin
signaling, likely via acting as Wnt coreceptors. How
Wnt activates
LRP5 /6/Arrow to initiate signal transduction
is not well defined.
Here we show that a PPPSP motif, which is
reiterated five times in the
LRP5 /6/Arrow intracellular domain, is
necessary and sufficient to
trigger Wnt/beta-catenin signaling. A single PPPSP
motif, upon transfer

to the LDL receptor, fully activates the Wnt pathway, inducing complete axis duplication in *Xenopus* and TCF/beta-catenin-responsive transcription in human cells. We further show that Wnt signal-ing stimulates, and requires, phosphorylation of the PPPSP motif, which creates an inducible docking site for Axin, a scaffolding protein controlling beta-catenin stability. Our study identifies a critical signaling module and a key phosphorylation-dependent activation step of the Wnt receptor complex and reveals a unifying logic for transmembrane signaling by Wnts, growth factors, and cytokines.

L7 ANSWER 32 OF 68 MEDLINE on STN
 DUPLICATE 13
 ACCESSION NUMBER: 2004639120 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15615112
 TITLE: The high bone mass family--the role of Wnt/ *****Lrp5*****

signaling in the regulation of bone mass.
 AUTHOR: Johnson M L
 CORPORATE SOURCE: Osteoporosis Research Center, Creighton University School of Medicine, Omaha, NE 68131, USA..
 MARKL@creighton.edu
 SOURCE: J Musculoskelet Neuronal Interact, (2004 Jun) 4 (2) 135-8.
 Ref: 23
 Journal code: 101084496. ISSN: 1108-

7161.
 PUB. COUNTRY: Greece
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200501
 ENTRY DATE: Entered STN: 20041224
 Last Updated on STN: 20050125
 Entered Medline: 20050124

AB A G171V mutation in the low-density lipoprotein receptor-related protein 5 (*****LRP5*****) was identified as causal for an autosomal dominant high bone mass trait in a single human family. A transgenic mouse line was produced that carries this mutation and develops a high bone mass phenotype that recapitulates the human phenotype. *****LRP5***** is a co-receptor for Wnt and we have investigated the potential role of this gene/protein and the Wnt signaling pathway in mediating the bone formation response to mechanical loading. The G171V mutation results in an increased responsiveness of bone to mechanical load and reduces the threshold of load required to elicit a response. Our studies have shown that the Wnt signaling pathway is activated in response to mechanical loading and this response is greatly enhanced in the presence of the G171V

mutation. Additionally, this mutation results in increased transcription of osteoprotegerin (OPG) in response to loading. Thus, the mutation appears to have direct effects at the level of the osteoblast and may also result in a reduction in osteoclastogenesis. The identification of *****LRP5***** Wnt signaling in bone mechanosensation has resulted in a new paradigm for understanding bone formation. Hopefully, knowledge gained from these studies will result in new therapies for treating osteoporosis.

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ACCESSION NUMBER: 2004057679 EMBASE
 TITLE: Expression of *****LDL*****
*****receptor***** - *****related***** *****protein***** *****5***** (*****LRP5*****

) as a novel marker for disease progression in high-grade osteosarcoma.
 AUTHOR: Hoang B.H.; Kubo T.; Healey J.H.; Sowers R.; Mazza B.; Yang R.; Huvo A.G.; Meyers P.A.; Gorlick R.
 CORPORATE SOURCE: R. Gorlick, Department of Pediatrics, Mem. Sloan-Kettering Cancer Center, Box 376, 1275 York Avenue, New York, NY 10021, United States

SOURCE: International Journal of Cancer, (10 Mar 2004) 109/1 (106-111).
 Refs: 32

ISSN: 0020-7136 CODEN: IJCNW
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 005 General Pathology and Pathological Anatomy

016 Cancer
 033 Orthopedic Surgery

LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB The Wingless-type (Wnt) family of proteins and its coreceptor *****LRP5*****

have recently been implicated in human skeletal development. Wnt pathway modulates cell fate and cell proliferation during embryonic development and carcinogenesis through activation of receptor-mediated signaling.

Osteosarcoma (OS) is a bone-forming tumor of mesenchymal origin whose growth control has been linked to autocrine or paracrine stimulation by several growth factor families. We examined 4 OS cell lines for WNT1, WNT4, WNT5A, WNT7A, WNT11, FZDI-10 and *****LRP5***** expression by reverse transcription polymerase chain reaction (RT-PCR). In addition, RT-PCR for *****LRP5***** expression was performed in 44 OS patient samples and the findings were correlated with clinical data. Expression

profiling of Wnts and their receptors revealed the presence of several isoforms in OS cell lines. Overall, 22/44 (50%) of OS patient samples showed evidence of ***LRP5*** expression. Presence of ***LRP5*** correlated significantly with tumor metastasis ($p = 0.005$) and the chondroblastic subtype of OS ($p = 0.045$). In addition, patients whose tumors were positive for ***LRP5*** showed a trend toward decreased event-free survival ($p = 0.066$). No significant association was found between ***LRP5*** expression and age, gender, site of disease, site of metastasis or degree of chemotherapy-induced tumor necrosis. Sequencing of exon 3 of ***LRP5*** in 10 OS patient-derived cell cultures showed no activating mutation of ***LRP5***. These results showed that expression of ***LRP5*** is a common event in OS and strongly suggest a role for LRP and Wnt signaling in the pathobiology and progression of this disease. .COPYRG.T. 2003 Wiley-Liss, Inc.

L7 ANSWER 34 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2004199481 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15095618
 TITLE: [Wnt/ ***LRP5*** , a new regulation osteoblastic pathway involved in reaching peak bone masses].
 Wnt/ ***LRP5*** , une nouvelle voie de regulation osteoblastique impliquee dans l'acquisition du pic de masses osseuses.
 AUTHOR: Caverzasio Joseph
 CORPORATE SOURCE: Service des maladies osseuses Departement de rehabilitation et geriatric HUG..
 Joseph.Caverzasio@medecine.unige.ch
 SOURCE: Revue medicale de la Suisse romande, (2004 Feb) 124 (2) 81-2.
 Journal code: 0421524. ISSN: 0035-3655.
 PUB. COUNTRY: Switzerland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: French
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200405
 ENTRY DATE: Entered STN: 20040421
 Last Updated on STN: 20040521
 Entered Medline: 20040520
 AB With the ageing of the population in industrial countries, osteoporosis became an important concern of public health. For an efficacious treatment of this disease, we would need drugs capable of selectively and safely increasing bone volume. Recent genetic analyses revealed a new signaling pathway involved in the regulation of osteoblastic cells and the acquisition of pic bone mass. Loss or gain of function mutations in the

LRP5 gene have been found to be associated with correspondingly low or high bone mass syndromes. Loss of function is associated with juvenile osteoporosis, whereas gain of function leads to the high bone mass syndrome. Recent studies have shown that ***LRP5*** is implicated in the regulation of the proliferation and of the activity of osteoblastic cells. By analogy with other cellular systems, it has been suggested that ***LRP5*** plays a role in the Wnt signaling system. ***Wnt*** ***proteins*** are known to be involved in developmental processes and the implication of this system in controlling osteoblastic activity and bone formation was completely unexpected. Analysis of the cellular mechanism by which Wnt/ ***LRP5*** activates osteoblastic cells is of potential interest for the development of new molecules capable of selectively increasing bone mass for the treatment of osteoporosis.

L7 ANSWER 35 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2004603043 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15576958
 TITLE: Recent topics on bone remodeling.
 AUTHOR: Shinoda Yusuke; Ogata Naoshi; Chung Ung II; Kawaguchi Hiroshi
 CORPORATE SOURCE: Department of Orthopaedic Surgery and Division of Tissue Engineering, University of Tokyo Hospital, Tokyo, Japan.
 SOURCE: Clin Calcium, (2004 Jan) 14 (1) 70-4.
 Ref: 28
 Journal code: 9433326. ISSN: 0917-5857.
 PUB. COUNTRY: Japan
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: Japanese
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200412
 ENTRY DATE: Entered STN: 20041204
 Last Updated on STN: 20041230
 Entered Medline: 20041229
 AB The Wnt signaling pathway has recently been demonstrated to play an important role in regulation of bone formation. ***LRP5*** is thought to signal through the canonical Wnt pathway. In humans, ***LRP5*** loss-of-function mutations lead to low bone mass with fractures, while ***LRP5*** gain-of-function mutations lead to high bone mass, thus identifying ***LRP5*** as an important regulator of bone mass. Patients with sclerosteosis have a severe skeletal disorder with progressive bone overgrowth due to a loss of function of the SOST gene, which implicates its role as a suppressor of bone formation. Recent study

revealed that SOST is a BMP antagonist with unique ligand specificity, negatively regulating bone formation by repressing BMP-induced osteoblast differentiation or function or both.

L7 ANSWER 36 OF 68 MEDLINE on STN
DUPLICATE 14
ACCESSION NUMBER: 2004030873 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14729180
TITLE: The ins and outs of Wingless signaling.
AUTHOR: Seto Elaine S; Bellen Hugo J
CORPORATE SOURCE: Program in Developmental
Biology, Department of Molecular
and Human Genetics, Division of
Neuroscience, Baylor
College of Medicine, Houston, TX 77030,
USA.
SOURCE: Trends in cell biology, (2004 Jan) 14
(1) 45-53. Ref: 71
Journal code: 9200566. ISSN: 0962-8924.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040121
Last Updated on STN: 20040820
Entered Medline: 20040819
AB Signaling through the highly conserved
Wingless/Wnt pathway plays a
crucial role in a diverse array of developmental
processes, many of which
depend upon the precise regulation of Wingless/Wnt
signaling levels.
Recent evidence has indicated that the intracellular
trafficking of
Wingless/Wnt signaling components can result in
significant changes in the
level of signaling. Here, we examine three
mechanisms through which
intracellular trafficking might regulate Wingless
signaling—the
degradation of Wingless, its transport and the
transduction of its signal.
The intracellular trafficking of several Wingless/Wnt
signaling
components, including ***LRP5***, LRP6,
Dishevelled and Axin, as well
as the functional implications of protein localization
on Wingless/Wnt
signaling, will be discussed.

L7 ANSWER 37 OF 68 MEDLINE on STN
DUPLICATE 15
ACCESSION NUMBER: 2004505926 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15474285
TITLE: Wnt signaling in osteoblasts and bone
diseases.
AUTHOR: Westendorf Jennifer J; Kahler Rachel
A; Schroeder Tania M
CORPORATE SOURCE: The Cancer Center and
Department of Orthopaedic Surgery,
University of Minnesota, MMC 806, 420
Delaware St. SE,
Minneapolis, MN 55455, USA..
weste047@umn.edu

SOURCE: Gene, (2004 Oct 27) 341 19-39. Ref:
219

Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20050114
Entered Medline: 20050113
AB Recent revelations that the canonical Wnt
signaling pathway promotes
postnatal bone accrual are major advances in our
understanding of skeletal
biology and bring tremendous promise for new
therapeutic treatments for
osteoporosis and other diseases of altered bone
mass. Wnts are soluble
glycoproteins that engage receptor complexes
composed of ***Lrp5*** /6
and Frizzled proteins. A subgroup of Wnts induces
a cascade of
intracellular events that stabilize beta-catenin,
facilitating its
transport to nuclei where it binds Lef1/Tcf
transcription factors and
alters gene expression to promote osteoblast
expansion and function.
Natural extracellular Wnt antagonists, Dickkopfs and
secreted
frizzled-related proteins, impair osteoblast function
and block bone
formation. In several genetic disorders of altered
skeletal mass,
mutations in ***LRP5*** create gain-of-function or
loss-of-function
receptors that are resistant to normal regulatory
mechanisms and cause
higher or lower bone density, respectively. In this
review, we summarize
the available molecular, cellular, and genetic data
that demonstrate how
Lrp5 and other components of the Wnt
signaling pathway influence
osteoblast proliferation, function, and survival. We
also discuss
regulatory mechanisms discovered in developmental
and tumor models that
may provide insights into novel therapies for bone
diseases.

L7 ANSWER 38 OF 68 CAPLUS COPYRIGHT 2005
ACS on STN
ACCESSION NUMBER: 2003:737597 CAPLUS
DOCUMENT NUMBER: 139:240388
TITLE: Novel application and function of
Wnt in the treatment
of diabetes and hyperlipemia
INVENTOR(S): Yamamoto, Tokuo; Sakai, Juro;
Fujino, Takahiro
PATENT ASSIGNEE(S): Angen MG, Inc., Japan
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE
APPLICATION NO. DATE

WO 2003075948 A1 20030918 WO 2003-
JP2719 20030307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG,
BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR,
KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NI, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ,
TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ,
UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY,
CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2002-64458
A 20020308

AB Drugs contg. ***Wnt*** ***protein*** or a gene
encoding
Wnt ***protein*** and having an effect of
promoting insulin
secretion or ameliorating lipid metab.; a method of
identifying an agonist
to ***LRP5*** /6; and a method of identifying a
compd. controlling the
expression of ***Wnt*** ***protein*** and
LRP5 /6 in
cells. The agonist and the compd. identified these
methods are useful in
treating or preventing, in particular, diabetes,
hyperlipemia or impaired
glucose tolerance, similar to drugs contg. Wnt.

REFERENCE COUNT: 9 THERE ARE 9 CITED
REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS
AVAILABLE IN THE RE FORMAT

L7 ANSWER 39 OF 68 USPATFULL on STN
ACCESSION NUMBER: 2003:330153
USPATFULL
TITLE: Diagnosis, prognosis and
identification of potential
therapeutic targets of multiple myeloma
based on gene
expression profiling

INVENTOR(S): Shaughnessy, John D., Little
Rock, AR, UNITED STATES
Barlogie, Bart, Little Rock, AR, UNITED
STATES
Zhan, Fenghuang, Little Rock, AR,
UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION: US 2003232364 A1
20031218
APPLICATION INFO.: US 2003-409004 A1
20030408 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser.
No. US 2002-289746, filed
on 7 Nov 2002, PENDING

NUMBER DATE

PRIORITY INFORMATION: US 2002-403075P
20020813 (60)

US 2001-348238P 20011107 (60)
US 2002-355386P 20020208 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Dr. Benjamin Adler,
ADLER & ASSOCIATES, 8011 Candle
Lane, Houston, TX, 77071

NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 4100

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Gene expression profiling between normal B
cells/plasma cells and
multiple myeloma cells revealed four distinct
subgroups of multiple
myeloma plasma cells that have significant
correlation with clinical
characteristics known to be associated with poor
prognosis. Diagnosis
for multiple myeloma (and possibly monoclonal
gammopathy of undetermined
significance) based on differential expression of 14
genes, as well as
prognostics for the four subgroups of multiple
myeloma based on the
expression of 24 genes were also established.
Gene expression profiling
also allows placing multiple myeloma into a
developmental schema
parallel to that of normal plasma cell differentiation.
The development
of a gene expression- or developmental stage-
based classification system
for multiple myeloma would lead to rational design
of more accurate and
sensitive diagnostics, prognostics and tumor-
specific therapies for
multiple myeloma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 40 OF 68 USPATFULL on STN
ACCESSION NUMBER: 2003:237344
USPATFULL
TITLE: Treatment involving Dkk-1 or
antagonists thereof
INVENTOR(S): DeAlmeida, Venita I., San
Carlos, CA, UNITED STATES
Stewart, Timothy A., San Francisco, CA,
UNITED STATES
PATENT ASSIGNEE(S): GENENTECH, INC. (U.S.
corporation)

NUMBER KIND DATE

PATENT INFORMATION: US 2003165501 A1
20030904
APPLICATION INFO.: US 2002-77065 A1
20020215 (10)

NUMBER DATE

PRIORITY INFORMATION: US 2001-269435P

20010216 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: GENENTECH, INC., 1

DNA WAY, SOUTH SAN FRANCISCO, CA,

94080

NUMBER OF CLAIMS: 52

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 17 Drawing Page(s)

LINE COUNT: 3365

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Antagonists to Dickkopf-1 (Dkk-1) protein are administered in effective

amounts to treat disorders involving insulin resistance, such as

non-insulin-dependent diabetes mellitus (NIDDM), hypoinsulinemia, and

disorders involving muscle atrophy, trauma, or degeneration. Preferably,

the antagonists are composed of compositions comprising antibodies

directed to Dkk-1 in a pharmaceutically acceptable carrier for use in

blocking the effects of Dkk-1. Additionally provided is a method of

treating obesity or hyperinsulinemia in a mammal by administering an

effective amount of Dkk-1 to a mammal. Also provided are methods of

diagnosing insulin resistance, hyper- and hypoinsulinemia, obesity, and

related disorders using Dkk-1 as a target and non-human transgenic

animals that overexpress dkk-1 nucleic acid.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 41 OF 68 USPATFULL on STN

ACCESSION NUMBER: 2003:237343

USPATFULL

TITLE: Wnt and frizzled receptors as targets for immunotherapy

in head and neck squamous cell

carcinomas

INVENTOR(S): Rhee, Chae-Seo, Seoul, KOREA, REPUBLIC OF

Sen, Malini, San Diego, CA, UNITED

STATES

Wu, Christina, San Diego, CA, UNITED

STATES

Leoni, Lorenzo M., San Diego, CA,

UNITED STATES

Corr, Maripat, San Diego, CA, UNITED

STATES

Carson, Dennis A., Del Mar, CA,

UNITED STATES

PATENT ASSIGNEE(S): REGENTS OF THE

UNIVERSITY OF CALIFORNIA, Oakland, CA

(non-U.S. corporation)

NUMBER KIND DATE

PATENT INFORMATION: US 2003165500 A1

20030904

APPLICATION INFO.: US 2002-285976 A1

20021101 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2002-US13802, filed

on 1 May 2002, PENDING

NUMBER DATE

PRIORITY INFORMATION: US 2001-287995P

20010501 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: TOWNSEND AND

TOWNSEND AND CREW, LLP, TWO

EMBARCADERO

CENTER, EIGHTH FLOOR, SAN

FRANCISCO, CA, 94111-3834

NUMBER OF CLAIMS: 140

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 33 Drawing Page(s)

LINE COUNT: 7969

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The diverse receptor-ligand pairs of the Wnt and frizzled (Fzd) families

play important roles during embryonic development, and thus may be

overexpressed in cancers that arise from immature cells. The mRNA levels

and expression levels of 5 Wnt (Wnt-1, 5a, 7a, 10b, 13) and 2 Fzd

(Fzd-2, 5) genes in 10 head and neck squamous carcinoma cell lines

(HNSCC) were investigated. In addition, anti-Wnt-1 antibodies were used

to study the Wnt/Fzd signalling pathway. These results indicate that

HNSCC cell lines overexpress one or more Wnt and Fzd genes, and the

proliferation and survival of a subset of HNSCC may depend on the

Wnt/Fzd pathway. Therefore, the Wnt and Fzd receptors may be useful

targets for immunotherapy of this common cancer.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 42 OF 68 USPATFULL on STN

ACCESSION NUMBER: 2003:37506 USPATFULL

TITLE: Regulator gene and system useful for the diagnosis and

therapy of osteoporosis

INVENTOR(S): Warman, Matthew L., Shaker Heights, OH, UNITED STATES

Gong, Yaoqin, Jinan, CHINA

Olsen, Bjorn R., Milton, MA, UNITED

STATES

Rawadi, Georges, Paris, FRANCE

Roman-Roman, Sergio, Paris, FRANCE

NUMBER KIND DATE

PATENT INFORMATION: US 2003027151 A1

20030206

APPLICATION INFO.: US 2001-931375 A1

20010817 (9)

NUMBER DATE

PRIORITY INFORMATION: US 2001-304851P

20010713 (60)

US 2000-226119P 20000818 (60)

US 2000-234337P 20000922 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: HELLER EHRMAN
WHITE & MCAULIFFE LLP, 1666 K STREET,NW,
SUITE 300, WASHINGTON, DC, 20006

NUMBER OF CLAIMS: 36

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 16 Drawing Page(s)

LINE COUNT: 3896

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A bone strength and mineralization regulatory
("BSMR") protein is

provided that can exist in multiple forms and that
affects bone density.

Polymorphic gene sequences of the protein are
provided that are

diagnostic of predisposition to osteoporosis. Other
detection tools,

compositions and methods of their use also are
provided for predicting,

evaluating and altering bone strength and
mineralization status. The

invention provides new natural and synthetic
pharmaceuticals that effect

the BSMR regulatory pathway and improve bone
status. Tools also are

provided for finding new pharmaceuticals that
operate by binding to BSMR

and that activate and/or deactivate this protein's
biological function

related to osteoporosis and blood vessel formation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 43 OF 68 MEDLINE on STN

ACCESSION NUMBER: 2003149709 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12551949

TITLE: Lymphoid enhancer factor-1 and beta-
catenin inhibit

Runx2-dependent transcriptional activation
of the

osteocalcin promoter.

AUTHOR: Kahler Rachel A; Westendorf

Jennifer J

CORPORATE SOURCE: University of Minnesota

Cancer Center, Department of

Orthopaedic Surgery and Graduate

Program in Microbiology,

Immunology and Cancer Biology,

Minneapolis, Minnesota

55455, USA.

SOURCE: Journal of biological chemistry, (2003
Apr 4) 278 (14)

11937-44.

Journal code: 2985121R. ISSN: 0021-

9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200305

ENTRY DATE: Entered STN: 20030401

Last Updated on STN: 20030520

Entered Medline: 20030519

AB Functional control of the transcription factor Runx2
is crucial for normal

bone formation. Runx2 is detectable throughout
osteoblast development and

maturation and temporally regulates several bone-
specific genes. In this

study, we identified a novel post-translational
mechanism regulating

Runx2-dependent activation of the osteocalcin
promoter. A functional

binding site for the high mobility group protein
lymphoid enhancer-binding

factor 1 (LEF1) was found adjacent to the proximal
Runx2-binding site in

the osteocalcin promoter. In transcription assays,
LEF1 repressed

Runx2-induced activation of the mouse osteocalcin
2 promoter in several

osteoblast lineage cell lines. Mutations in the LEF1-
binding site

increased the basal activity of the osteocalcin
promoter; however, the

LEF1 recognition site in the osteocalcin promoter
was surprisingly not

required for LEF1 repression. A novel interaction
between the DNA-binding

domains of Runx2 and LEF1 was identified and
found crucial for

LEF1-mediated repression of Runx2. LEF1 is a
nuclear effector of the Wnt/

LRP5 /beta-catenin signaling pathway, which
is also essential for

osteoblast proliferation and normal skeletal
development. A

constitutively active beta-catenin enhanced LEF1-
dependent repression of

Runx2. These data identify a novel mechanism of
regulating Runx2 activity

in osteoblasts and link Runx2 transcriptional activity
to beta-catenin

signaling.

L7 ANSWER 44 OF 68 MEDLINE on STN

DUPLICATE 16

ACCESSION NUMBER: 2003508144 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14584895

TITLE: BMP-2 controls alkaline phosphatase
expression and

osteoblast mineralization by a Wnt
autocrine loop.

AUTHOR: Rawadi Georges; Vayssiere Beatrice;
Dunn Fred; Baron

Roland; Roman-Roman Sergio

CORPORATE SOURCE: Proskelia Pharmaceuticals,
Romainville, France..

georges.rawadi@proskelia.com

SOURCE: Journal of bone and mineral research
: official journal of

the American Society for Bone and Mineral
Research, (2003

Oct) 18 (10) 1842-53.

Journal code: 8610640. ISSN: 0884-0431.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200406

ENTRY DATE: Entered STN: 20031031

Last Updated on STN: 20040603

Entered Medline: 20040602

AB Wnt/beta-catenin signaling has recently been
suggested to be involved in

bone biology. The precise role of this cascade in
osteoblast

differentiation was examined. We show that a Wnt autocrine loop mediates the induction of alkaline phosphatase and mineralization by BMP-2 in pre-osteoblastic cells. INTRODUCTION: Loss of function of ***LRP5*** leads to osteoporosis (OPPG syndrome), and a specific point mutation in this same receptor results in high bone mass (HBM). Because ***LRP5*** acts as a coreceptor for ***Wnt*** ***proteins***, these findings suggest a crucial role for Wnt signaling in bone biology. MATERIALS AND METHODS: We have investigated the involvement of the Wnt/ ***LRP5*** cascade in osteoblast function by using the pluripotent mesenchymal cell lines C3H10T1/2, C2C12, and ST2 and the osteoblast cell line MC3T3-E1. Transfection experiments were carried out with a number of elements of the Wnt/ ***LRP5*** pathway. Measuring osteoblast and adipocyte differentiation markers addressed the effect of this cascade on osteoblast differentiation. RESULTS: In mesenchymal cells, only Wnt's capable of stabilizing beta-catenin induced the expression of alkaline phosphatase (ALP). Wnt3a-mediated ALP induction was inhibited by overexpression of either Xdd1, dickkopf 1 (dkk1), or LRP5deltaC, indicating that canonical beta-catenin signaling is responsible for this activity. The use of Noggin, a bone morphogenetic protein (BMP) inhibitor, or cyclopamine, a Hedgehog inhibitor, revealed that the induction of ALP by Wnt is independent of these morphogenetic proteins and does not require de novo protein synthesis. In contrast, blocking Wnt/ ***LRP5*** signaling or protein synthesis inhibited the ability of both BMP-2 and Shh to induce ALP in mesenchymal cells. Moreover, BMP-2 enhanced Wnt1 and Wnt3a expression in our cells. In MC3T3-E1 cells, where endogenous ALP levels are maximal, antagonizing the Wnt/ ***LRP5*** pathway led to a decrease of ALP activity. In addition, overexpression of dkk1 reduced extracellular matrix mineralization in a BMP-2-dependent assay. CONCLUSIONS: Our data strongly suggest that the capacity of BMP-2 and Shh to induce ALP relies on Wnt expression and the Wnt/ ***LRP5*** signaling cascade. Moreover the effects of BMP-2 on extracellular matrix mineralization by osteoblasts are mediated, at least in part, by the induction of a Wnt autocrine/paracrine loop. These results may help to explain the phenotype of OPPG patients and HBM.

L7 ANSWER 45 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN DUPLICATE 17
 ACCESSION NUMBER: 2003141629 EMBASE
 TITLE: Wnt signaling in B-cell neoplasia.
 AUTHOR: Qiang Y.-W.; Endo Y.; Rubin J.S.; Rudikoff S.
 CORPORATE SOURCE: S. Rudikoff, Lab. of Cell. and Molecular Biology, National Cancer Institute, NIH, Bethesda, MD 20892, United States.
 SOURCE: Oncogene, (13 Mar 2003) 22/10 (1536-1545).
 Refs: 39
 ISSN: 0950-9232 CODEN: ONCNES

COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 016 Cancer
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB Wnts comprise a family of secreted proteins that interact with receptors consisting of a Frizzled (Fz) family member alone or complexed with LDL receptor-related proteins (***LRP5*** /6). Wnt signaling plays a crucial role in both development and differentiation, and activation of a 'canonical' Wnt pathway resulting in .beta.-catenin stabilization is associated with several types of human cancers. To date, little is known about potential Wnt signaling in mature lymphocytes or lymphoid neoplasia. Herein, we have analysed Wnt signaling in mature B cells (lymphomas) and plasma cells (multiple myeloma). Both Fz and ***LRP5*** /6 mRNAs were expressed in myeloma lines, but ***LRP5*** /6 were not observed in lymphomas. In myelomas, a canonical Wnt signaling pathway was activated following treatment with Wnt-3a as assessed by accumulation of .beta.-catenin, but .beta.-catenin levels actually decreased in lymphoma cells. Wnt-3a treatment further led to striking morphological changes in myeloma cells accompanied by rearrangement of the actin cytoskeleton. Morphological changes were associated with a second Wnt pathway dependent on Rho activation. These results suggest that Wnt responsiveness is a stage-specific phenomenon in B-cell development and that the morphological changes associated with Wnt signaling may play a role in the motility and metastatic potential of myeloma cells.

L7 ANSWER 46 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN DUPLICATE 18
 ACCESSION NUMBER: 2003424757 EMBASE
 TITLE: High Bone Mass in Mice Expressing a Mutant ***LRP5*** Gene.
 AUTHOR: Babij P.; Zhao W.; Small C.; Kharode Y.; Yaworsky P.J.; Boussein M.L.; Reddy P.S.; Bodine P.V.; Robinson J.A.; Bhat

B.; Marzolf J.; Moran R.A.; Bex F.
CORPORATE SOURCE: Dr. F. Bex, Women's Health
Research Institute, Wyeth
Research, 500 Arcola Road, Collegeville,
PA 19426, United

States. bexf@wyeth.com
SOURCE: Journal of Bone and Mineral
Research, (1 Jun 2003) 18/6
(960-974).

Refs: 46

ISSN: 0884-0431 CODEN: JBMREJ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology

029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A unique mutation in ***LRP5*** is associated
with high bone mass in

man. Transgenic mice expressing this ***LRP5***
mutation have a

similar phenotype with high bone mass and
enhanced strength. These results

underscore the importance of ***LRP5*** in
skeletal regulation and

suggest targets for therapies for bone disease. A
mutation (G171V) in the

low-density lipoprotein receptor related protein 5 (
LRP5) has

been associated with high bone mass (HBM) in two
independent human

kindreds. To validate the role of the mutation,
several lines of

transgenic mice were created expressing either the
human ***LRP5***

G171V substitution or the wildtype ***LRP5***
gene in bone. Volumetric

bone mineral density (vBMD) analysis by pQCT
showed dramatic increases in

both total vBMD (30-55%) and trabecular vBMD
(103-250%) of the distal

femoral metaphysis and increased cortical size of
the femoral diaphysis in

mutant G171V transgenics at 5, 9, 17, 26, and 52
weeks of age (p < 0.01

for all). In addition, high-resolution microcomputed
tomography (microCT)

analysis of the distal femorae and lumbar vertebrae
revealed an increase

(110-232%) in trabecular bone volume fraction
caused by both increased

trabecular number (41-74%) and increased
trabecular thickness (34-46%; p <

0.01 for all) in the mutant G171V mice. The
increased bone mass was

associated with significant increases in vertebral
compressive strength

(80-140%) and the increased cortical size with
significant increases in

femoral bending strength (50-130%). There were no
differences in

osteoclast number at 17 weeks of age. However,
compared with littermate

controls, the mutant G171V transgenic mice showed
an increase in actively

mineralizing bone surface, enhanced alkaline
phosphatase staining in

osteoblasts, and a significant reduction in the
number of TUNEL-positive

osteoblasts and osteocytes. These results suggest
that the increased bone
mineral density in mutant G171V mice was caused
by increased numbers of
active osteoblasts, which could in part be because of
their increased

functional lifespan. While slight bone anabolic
activity was observed from

overexpression of the wildtype ***LRP5*** gene, it
is clear that the

G171V mutation, rather than overexpression of the
receptor itself, is

primarily responsible for the dramatic HBM bone
effects. Together, these

findings establish the importance of this novel and
unexpected role of a

lipoprotein receptor in regulating bone mass and
afford a new model to

explore ***LRP5*** and its recent association with
Wnt signaling in

bone biology.

L7 ANSWER 47 OF 68 BIOSIS COPYRIGHT (c)
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STN DUPLICATE 19

ACCESSION NUMBER: 2003:202905 BIOSIS

DOCUMENT NUMBER: PREV200300202905

TITLE: Wg/Wnt signal can be transmitted
through Arrow/ ***LRP5***

,6 and Axin independently of
Zw3/Gsk3beta activity.

AUTHOR(S): Tolwinski, Nicholas S.; Wehrli,
Marcel; Rives, Anna;

Erdeniz, Naz; DiNardo, Stephen;
Wieschaus, Eric [Reprint

Author]

CORPORATE SOURCE: Howard Hughes Medical
Institute, Princeton University,

Princeton, NJ, 08544, USA

ewieschaus@molbio.princeton.edu

SOURCE: Developmental Cell, (March 2003)
Vol. 4, No. 3, pp.

407-418, print.

ISSN: 1534-5807 (ISSN print).

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 23 Apr 2003

Last Updated on STN: 23 Apr 2003

AB Activation of the Wnt signaling cascade provides
key signals during

development and in disease. Here we provide
evidence, by designing a Wnt

receptor with ligand-independent signaling activity,
that physical

proximity of Arrow (LRP) to the Wnt receptor

Frizzled-2 triggers the

intracellular signaling cascade. We have uncovered
a branch of the Wnt

pathway in which Amadillo activity is regulated
concomitantly with the

levels of Axin protein. The intracellular pathway
bypasses Gsk3beta/Zw3,

the kinase normally required for controlling beta-
catenin/Amadillo

levels, suggesting that modulated degradation of
Amadillo is not required

for Wnt signaling. We propose that Arrow (LRP)
recruits Axin to the

membrane, and that this interaction leads to Axin
degradation. As a

consequence, Armadillo is no longer bound by Axin, resulting in nuclear signaling by Armadillo.

L7 ANSWER 48 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN DUPLICATE 20
ACCESSION NUMBER: 2003070945 EMBASE
TITLE: MESD encodes an ***LRP5*** /6
chaperone essential for

specification of mouse embryonic polarity.
AUTHOR: Hsieh J.-C.; Lee L.; Zhang L.; Wefer S.; Brown K.; DeRossi C.; Wines M.E.; Rosenquist T.; Holdener B.C.

CORPORATE SOURCE: B.C. Holdener, Dept. of Biochem. and Cell Biology, Center for Developmental Genetics, State University of New York, Stony Brook, NY 11794, United States. bernadette.holdener@stonybrook.edu
SOURCE: Cell, (7 Feb 2003) 112/3 (355-367).
Refs: 39
ISSN: 0092-8674 CODEN: CELLB5

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Specification of embryonic polarity and pattern formation in multicellular organisms requires inductive signals from neighboring cells. One approach toward understanding these interactions is to study mutations that disrupt development. Here, we demonstrate that mesd, a gene identified in the mesoderm development (mesd) deletion interval on mouse chromosome 7, is essential for specification of embryonic polarity and mesoderm induction. MESD functions in the endoplasmic reticulum as a specific chaperone for ***LRP5*** and LRP6, which in conjunction with Frizzled, are coreceptors for canonical WNT signal transduction. Disruption of embryonic polarity and mesoderm differentiation in mesd-deficient embryos likely results from a primary defect in WNT signaling. However, phenotypic differences between mesd-deficient and wnt3(-/-) embryos suggest that MESD may function on related members of the low-density lipoprotein receptor (LDLR) family, whose members mediate diverse cellular processes ranging from cargo transport to signaling.

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ACCESSION NUMBER: 2003:278772 BIOSIS
DOCUMENT NUMBER: PREV200300278772
TITLE: The ***LRP5*** gene is involved in different conditions with an increased bone density as illustrated by the identification of six novel missense mutations.

AUTHOR(S): Van Wesenbeeck, L. [Reprint Author]; Cleiren, E. [Reprint Author]; Gram, J.; Beals, R. K.; Warman, M. L.; deVernejoul, M. C.; Bollerslev, J.; Van Hul, W. [Reprint Author]

CORPORATE SOURCE: Dept. Medical Genetics, University of Antwerp, Antwerp, Belgium

SOURCE: Calcified Tissue International, (April 2003) Vol. 72, No. 4, pp. 327. print.
Meeting Info.: 30th European Symposium on Calcified

Tissues. Rome, Italy. May 08-12, 2003.
CODEN: CTINDZ. ISSN: 0171-967X.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003

L7 ANSWER 50 OF 68 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:278720 BIOSIS
DOCUMENT NUMBER: PREV200300278720
TITLE: Role of the WNT/ ***LRP5*** pathway in regulation of

bone mass and osteoblast function.
AUTHOR(S): Warman, M. [Reprint Author]
CORPORATE SOURCE: Cleveland, OH, USA
SOURCE: Calcified Tissue International, (April 2003) Vol. 72, No. 4, pp. 314. print.
Meeting Info.: 30th European Symposium on Calcified

Tissues. Rome, Italy. May 08-12, 2003.
CODEN: CTINDZ. ISSN: 0171-967X.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jun 2003
Last Updated on STN: 11 Jun 2003

L7 ANSWER 51 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN DUPLICATE 21
ACCESSION NUMBER: 2003162201 EMBASE
TITLE: Axin and the Axin/Arrow-binding protein DCAP mediate

glucose-glycogen metabolism.
AUTHOR: Yamazaki H.; Yanagawa S.-I.
CORPORATE SOURCE: H. Yamazaki, Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, United States. hyamazaki@hms.harvard.edu

SOURCE: Biochemical and Biophysical Research Communications, (2 May 2003) 304/2 (229-235).
Refs: 33
ISSN: 0006-291X CODEN: BBRCA

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry
LANGUAGE: English

SUMMARY LANGUAGE: English
 AB Axin was found as a negative regulator of the canonical Wnt pathway. Human ***LRP5*** was originally found as a candidate gene of insulin dependent diabetes mellitus (IDDM), but its Drosophila homolog, Arrow, works as a co-receptor of the canonical Wnt signal. In our previous paper, we found a new Drosophila Axin (Daxin)-binding SH3 protein, DCAP, a homolog of mammalian CAV family protein. Among the subtypes, DCAPL3 shows significant homology with CAP, an essential component of glucose transport in insulin signal. Further binding assay revealed that DCAP binds to not only Axin but also Arrow, and Axin binds to not only GSK3.beta. but also Arrow. However, overexpression and RNAi experiments of DCAP do not affect the canonical Wnt pathway. As DCAP is expressed predominantly in insulin-target organs, and as RNAi of DCAP disrupts the pattern of endogenous glycogen accumulation in late stage embryos, we suggest that DCAP is also involved in glucose transport. Moreover, early stage embryos lacking maternal Axin show significant delay of initial glycogen decomposition, and RNAi of Axin in S2 cells revealed quite increase of endogenous glycogen level as well as GSK3.beta.. These results suggest that Axin and DCAP mediate glucose-glycogen metabolism in embryo. In addition, the interaction among Axin, Arrow, and DCAP implies a possible cross-talk between Wnt signal and insulin signal.
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L7 ANSWER 52 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN
 ACCESSION NUMBER: 2003030437 EMBASE
 TITLE: Low-density lipoprotein receptor-related protein 5 (***LRP5***) is essential for normal cholesterol metabolism and glucose-induced insulin secretion.
 AUTHOR: Fujino T.; Asaba H.; Kang M.-J.; Ikeda Y.; Sone H.; Takada S.; Kim D.-H.; Ioka R.X.; Ono M.; Tomoyori H.; Okubo M.; Murase T.; Kamataki A.; Yamamoto J.; Magoori K.; Takahashi S.; Miyamoto Y.; Oishi H.; Nose M.; Okazaki M.; Usui S.; Imaizumi K.; Yanagisawa M.; Sakai J.; Yamamoto T.T.
 CORPORATE SOURCE: J. Sakai, Yanagisawa Orphan Receptor Project, Exploratory Res. for Adv. Technology, Japan Sci. and Technol. Corporation, 2-41, Aomi, Koto-ku, Tokyo 135-0064, Japan.
 jmsakai@mail.cc.tohoku.ac.jp

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (7 Jan 2003) 100/1 (229-234).

Refs: 39
 ISSN: 0027-8424 CODEN: PNASA6
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 003 Endocrinology 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB A Wnt coreceptor low-density lipoprotein receptor-related protein 5 (***LRP5***) plays an essential role in bone accrual and eye development. Here, we show that ***LRP5*** is also required for normal cholesterol and glucose metabolism. The production of mice lacking ***LRP5*** revealed that ***LRP5*** deficiency led to increased plasma cholesterol levels in mice fed a high-fat diet, because of the decreased hepatic clearance of chylomicron remnants. In addition, when fed a normal diet, ***LRP5*** -deficient mice showed a markedly impaired glucose tolerance. The LRPS-deficient islets had a marked reduction in the levels of intracellular ATP and Ca(2+) in response to glucose, and thereby glucose-induced insulin secretion was decreased. The intracellular inositol 1,4,5-trisphosphate (IP3) production in response to glucose was also reduced in ***LRP5*** -/- islets. Real-time PCR analysis revealed a marked reduction of various transcripts for genes involved in glucose sensing in ***LRP5*** -/- islets. Furthermore, exposure of ***LRP5*** +/- islets to Wnt-3a and Wnt-5a stimulates glucose-induced insulin secretion and this stimulation was blocked by the addition of a soluble form of Wnt receptor, secreted Frizzled-related protein-1. In contrast, ***LRP5*** -deficient islets lacked the Wnt-3a-stimulated insulin secretion. These data suggest that Wnt/ ***LRP5*** signaling contributes to the glucose-induced insulin secretion in the islets.

L7 ANSWER 53 OF 68 MEDLINE on STN
 DUPLICATE 22
 ACCESSION NUMBER: 2003285530 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12812787
 TITLE: A role for Wnt/beta-catenin signaling in lens epithelial differentiation.
 AUTHOR: Stump Richard J W; Ang Sharyn; Chen Yongjuan; von Bahr Tatiana; Lovicu Frank J; Pinson Kathleen; de Jongh Robbert U; Yamaguchi Terry P; Sassoon David A; McAvoy John W
 CORPORATE SOURCE: Save Sight Institute, The University of Sydney, Sydney

Hospital & Eye Hospital, GPO Box 4337,
NSW 2006, Australia.
CONTRACT NUMBER: R01 EYO3177 (NEI)
SOURCE: Developmental biology, (2003 Jul 1)
259 (1) 48-61.

Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030619
Last Updated on STN: 20030723
Entered Medline: 20030722

AB The differentiation of epithelial cells and fiber cells
from the anterior
and posterior compartments of the lens vesicle,
respectively, give the
mammalian lens its distinctive polarity. While much
progress has been
made in understanding the molecular basis of fiber
differentiation, little
is known about factors that govern the differentiation
of the epithelium.
Members of the Wnt growth factor family appear to
be key regulators of
epithelial differentiation in various organ systems.
Wnts are ligands for
Frizzled receptors and can activate several signaling
pathways, of which
the best understood is the Wnt/beta-catenin
pathway. The presence of
LDL-related protein coreceptors (LRPs) 5 or 6 has
been shown to be a
requirement for Wnt signaling through the beta-
catenin pathway. To access
the role of this signaling pathway in the lens, we
analyzed mice with a
null mutation of *lrp6*. These mice had small eyes
and aberrant lenses,
characterized by an incompletely formed anterior
epithelium resulting in
extrusion of the lens fibers into the overlying corneal
stroma. We also
showed that multiple Wnts, including 5a, 5b, 7a, 7b,
8a, 8b, and Frizzled
receptors 1, 2, 3, 4, and 6, were detected in the lens.
Expression of
these molecules was generally present throughout
the lens epithelium and
extended into the transitional zone, where early fiber
elongation occurs.
In addition to both ***LRP5*** and LRP6, we also
showed the expression
of other molecules involved in Wnt signaling and its
regulation, including
Dishevelleds, Dickkopfs, and secreted Frizzled-
related proteins. Taken
together, these results indicate a role for Wnt
signaling in regulating
the differentiation and behavior of lens cells.

L7. ANSWER 54 OF 68 CAPLUS COPYRIGHT 2005
ACS on STN
ACCESSION NUMBER: 2004:841503 CAPLUS
TITLE: Secreted antagonists/modulators of
Wnt signaling
AUTHOR(S): Semenov, Mikhail V.; He, Xi

CORPORATE SOURCE: Division of Neuroscience,
Department of Neurology,
Children's Hospital/Harvard Medical
School, Boston,
MA, USA
SOURCE: Wnt Signaling in Development
(2003), 15-34.
Editor(s): Kuehl, Michael. Landes
Bioscience:
Georgetown, Tex.
CODEN: 69FYH5; ISBN: 0-306-47838-

2
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Wnt signaling is controlled by a plethora of
extracellular modulators that
bind either Wnt mols. or Wnt receptors. These
modulators in most cases
function to antagonize Wnt signaling and in concept
define the range,
amplitude, and duration of Wnt signaling. Four
conserved but structurally
distinct families of Wnt antagonists are currently
known from lower
vertebrates to human: sFRP (secreted frizzled
related protein), WIF-1
(Wnt-inhibitory factor 1), Cerberus, and Dickkopf
(Dkk). SFRP proteins,
WIF-1 and Cerberus have been shown to bind Wnt
mols. and may inhibit
multiple signaling pathways activated by these Wnt
mols. ***Dkk***
proteins bind to the Wnt co-receptor
LRP5 /LRP6, and
specifically inhibit (but in some cases stimulate)
LRP5
/LRP6-dependent Wnt/beta.-catenin signaling. In
Drosophila, secreted
Wingful/Notum antagonizes Wingless (Wnt)
signaling by functioning as a
modifying enzyme for Dally and Dally-like,
proteoglycans that may
facilitate the Wnt receptor interaction. Secreted Wnt
antagonists play
crit. roles in embryogenesis and are implicated in
variety of physiol. and
pathol. processes.
REFERENCE COUNT: 109 THERE ARE 109
CITED REFERENCES AVAILABLE FOR
THIS RECORD. ALL CITATIONS
AVAILABLE IN THE RE
FORMAT

L7 ANSWER 55 OF 68 MEDLINE on STN
ACCESSION NUMBER: 2004233774 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12729465
TITLE: Wnt/Wingless signaling through beta-
catenin requires the
function of both LRP/Arrow and frizzled
classes of
receptors.
AUTHOR: Schweizer Liang; Varmus Harold
CORPORATE SOURCE: Cell Biology Program,
Sloan-Kettering Institute for Cancer
Research, 1275 York Avenue, New York,
NY 10021, USA..
schweizl@mskcc.org
SOURCE: BMC cell biology [electronic
resource], (2003 May 2) 4 (1)
4.

Journal code: 100966972. ISSN: 1471-2121.

PUB. COUNTRY: England; United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20040511
Last Updated on STN: 20050122
Entered Medline: 20050121

AB BACKGROUND: Wnt/Wingless (Wg) signals are transduced by seven-transmembrane Frizzleds (Fzs) and the single-transmembrane ***LDL*** - ***receptor*** - ***related*** ***proteins*** ***5*** or 6 (***LRP5*** /6) or Arrow. The aminoterminals of LRP and Fz were reported to associate only in the presence of Wnt, implying that Wnt ligands form a trimeric complex with two different receptors. However, it was recently reported that LRPs activate the Wnt/beta-catenin pathway by binding to Axin in a Dishevelled-independent manner, while Fzs transduce Wnt signals through Dishevelled to stabilize beta-catenin. Thus, it is possible that ***Wnt*** ***proteins*** form separate complexes with Fzs and LRPs, transducing Wnt signals separately, but converging downstream in the Wnt/beta-catenin pathway. The question then arises whether both receptors are absolutely required to transduce Wnt signals. RESULTS: We have established a sensitive luciferase reporter assay in Drosophila S2 cells to determine the level of Wg-stimulated signaling. We demonstrate here that Wg can synergize with DFz2 and function cooperatively with LRP to activate the beta-catenin/Armadillo signaling pathway. Double-strand RNA interference that disrupts the synthesis of either receptor type dramatically impairs Wg signaling activity. Importantly, the pronounced synergistic effect of adding Wg and DFz2 is dependent on Arrow and Dishevelled. The synergy requires the cysteine-rich extracellular domain of DFz2, but not its carboxyterminus. Finally, mammalian LRP6 and its activated forms, which lack most of the extracellular domain of the protein, can activate the Wg signaling pathway and cooperate with Wg and DFz2 in S2 cells. We also show that the aminoterminal of LRP/Arr is required for the synergy between Wg and DFz2.

CONCLUSION: Our study indicates that Wg signal transduction in S2 cells depends on the function of both LRPs and DFz2, and the results are consistent with the proposal that Wnt/Wg signals through the aminoterminal

domains of its dual receptors, activating target genes through Dishevelled.

L7 ANSWER 56 OF 68 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2003:323467 BIOSIS
DOCUMENT NUMBER: PREV200300323467
TITLE: Wnt/Wingless signaling through beta-catenin requires the function of both LRP/Arrow and Frizzled classes of receptors.

AUTHOR(S): Schweizer, Liang [Reprint Author]; Varmus, Harold
CORPORATE SOURCE: Cell Biology Program, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY, 10021, USA
schweizl@mskcc.org; varmus@mskcc.org

SOURCE: BMC Cell Biology, (May 2 2003) Vol. 4, No. 4 Cited June 13, 2003. <http://www.biomedcentral.com/1471-2121>. online.

ISSN: 1471-2121 (ISSN online).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Jul 2003
Last Updated on STN: 9 Jul 2003

AB Background: Wnt/Wingless (Wg) signals are transduced by seven-transmembrane Frizzleds (Fzs) and the single-transmembrane LDL-receptor-3related proteins 5 or 6 (***LRP5*** /6) or Arrow. The aminoterminals of LRP and Fz were reported to associate only in the presence of Wnt, implying that Wnt ligands form a trimeric complex with two different receptors. However, it was recently reported that LRPs activate the Wnt/beta-catenin pathway by binding to Axin in a Dishevelled-independent manner, while Fzs transduce Wnt signals through Dishevelled to stabilize beta-catenin. Thus, it is possible that ***Wnt*** ***proteins*** form separate complexes with Fzs and LRPs, transducing Wnt signals separately, but converging downstream in the Wnt/beta-catenin pathway. The question then arises whether both receptors are absolutely required to transduce Wnt signals. Results: We have established a sensitive luciferase reporter assay in Drosophila S2 cells to determine the level of Wg-stimulated signaling. We demonstrate here that Wg can synergize with DFz2 and function cooperatively with LRP to activate the beta-catenin/Armadillo signaling pathway. Double-strand RNA interference that disrupts the synthesis of either receptor type dramatically impairs Wg signaling activity. Importantly, the pronounced synergistic effect of adding Wg and DFz2 is dependent on Arrow and Dishevelled. The synergy

requires the cysteine-rich extracellular domain of DFz2, but not its carboxyterminus. Finally, mammalian LRP6 and its activated forms, which lack most of the extracellular domain of the protein, can activate the Wg signaling pathway and cooperate with Wg and DFz2 in S2 cells. We also show that the aminoterminal of LRP/Arr is required for the synergy between Wg and DFz2. Conclusion: Our study indicates that Wg signal transduction in S2 cells depends on the function of both LRPs and DFz2, and the results are consistent with the proposal that Wnt/Wg signals through the aminoterminal domains of its dual receptors, activating target genes through Dishevelled.

L7 ANSWER 57 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2002275003 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12015398
 TITLE: Regulation of bone formation and vision by ***LRP5***
 COMMENT: Comment on: N Engl J Med. 2002 May 16;346(20):1513-21.
 PubMed ID: 12015390
 AUTHOR: Patel Millan S; Karsenty Gerard
 SOURCE: New England journal of medicine, (2002 May 16) 346 (20) 1572-4.
 Journal code: 0255562. ISSN: 1533-4406.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Commentary
 Editorial
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Space Life Sciences
 ENTRY MONTH: 200205
 ENTRY DATE: Entered STN: 20020517
 Last Updated on STN: 20020623
 Entered Medline: 20020522

L7 ANSWER 58 OF 68 MEDLINE on STN
 DUPLICATE 23
 ACCESSION NUMBER: 2002470888 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12121999
 TITLE: A novel set of Wnt-Frizzled fusion proteins identifies receptor components that activate beta - catenin-dependent signaling.
 AUTHOR: Holmen Sheri L; Salic Adrian; Zylstra Cassandra R;
 Kirschner Marc W; Williams Bart O
 CORPORATE SOURCE: Laboratory of Cell Signaling and Carcinogenesis, Van Andel Research Institute, Grand Rapids, Michigan 49503, USA.
 SOURCE: Journal of biological chemistry, (2002 Sep 20) 277 (38) 34727-35.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English

FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200210
 ENTRY DATE: Entered STN: 20020917
 Last Updated on STN: 20030105
 Entered Medline: 20021024
 AB ***Wnt*** ***proteins*** initiate the canonical (beta-catenin-regulated) signaling cascade by binding to seven-transmembrane spanning receptors of the Frizzled (Fz) family together with the coreceptors ***LRP5*** and -6, members of the low density lipoprotein receptor-related protein family (LRP). Several reports have shown physical and functional associations between various Wnt, LRP, and Frizzled molecules; however, the underlying mechanisms for selectivity remain poorly understood. We present data on a novel set of Wnt-Fz fusion constructs that are useful for elucidating mechanisms of Wnt signal transduction specificity in both Xenopus embryos and 293T cells. In 293T cells, coexpression of several Wnt-Fz fusion proteins with LRP6, but not ***LRP5***, significantly activated a Wnt-responsive promoter. Optimized TOPFlash. Interestingly, ***Wnt*** ***proteins*** from both the Wnt1 and Wnt5A classes, when fused to the same Frizzled, can synergize with LRP6 to activate signaling and induce secondary axes in Xenopus embryos. However, when several Wnt-Fz constructs containing different Frizzled molecules were tested, it was found that all Frizzled molecules are not equivalent in their ability to activate the canonical Wnt pathway in this context. The data suggest that the distinction between the two Wnt classes lies not in intrinsic differences in the molecules but via the Frizzled molecules with which they interact.

L7 ANSWER 59 OF 68 MEDLINE on STN
 DUPLICATE 24
 ACCESSION NUMBER: 2002283362 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11884395
 TITLE: Casein kinase I and casein kinase II differentially regulate axin function in Wnt and JNK pathways.
 AUTHOR: Zhang Yi; Qiu Wen-Jie; Chan Siu Chiu; Han Jiahuai; He Xi;
 Lin Sheng-Cai
 CORPORATE SOURCE: Department of Biochemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China.
 SOURCE: Journal of biological chemistry, (2002 May 17) 277 (20) 17706-12.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020528
Last Updated on STN: 20030105
Entered Medline: 20020716

AB Axin uses different combinations of functional domains in down-regulation of the Wnt pathway and activation of the MEKK1/JNK pathway. We are interested in the elucidation of the functional switch of Axin. In the present study, we show that the Wnt activator CKIepsilon, but not CKIalpha, Frat1, ***LRP5***, or LRP6, inhibited Axin-mediated JNK activation. We also found that both CKIalpha and CKIepsilon interacted with Axin, whereas CKIalpha did not bind to Axin and had no effect on Axin-mediated JNK activity even though CKIalpha has also been suggested to be an activator for the Wnt pathway. The COOH-terminal region and the MEKK1-interacting domain of Axin are important for CKIalpha-Axin and CKIepsilon-Axin interaction. We further demonstrated that CKIepsilon and CKIalpha binding to Axin excluded MEKK1 binding, indicating that a competitive physical occupancy may underlie the inhibitory effect. Moreover, our data indicated that CKIepsilon kinase activity plays an additive role in this effect. Taken together, we have demonstrated that CKI and CKII exhibit differential effects on Axin-MEKK1 interaction and Axin-mediated JNK activation. Furthermore, our data suggest that CKI may provide a possible switch mechanism for Axin function in the regulation of Wnt and JNK pathways.

L7 ANSWER 60 OF 68 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 25
ACCESSION NUMBER: 2002:360588 CAPLUS
DOCUMENT NUMBER: 137:291952
TITLE: Regulation of bone formation and vision by

LRP5
AUTHOR(S): Patel, Millan S.; Karsenty, Gerard
CORPORATE SOURCE: Baylor College Med., Houston, TX, 77030, USA
SOURCE: New England Journal of Medicine (2002), 346(20),

1572-1574
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review on the lock-and-key mechanism involving low d. lipoprotein receptor-related protein 5 (***LRP5***) that regulates bone formation and vision. Carriers of ***LRP5*** loss-of-function mutations have a lower bone mass than noncarriers, suggesting that the effects of this gene

are dominant for the regulation of bone mass. Secreted proteins from the Dickkopf family bind with high affinity to ***LRP5*** or its closely related homolog, LRP6, and thus directly prevent binding of ***Wnt*** ***proteins***.

REFERENCE COUNT: 18 THERE ARE 18
CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS
AVAILABLE IN THE RE FORMAT

L7 ANSWER 61 OF 68 MEDLINE on STN
ACCESSION NUMBER: 2002274995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12015390
TITLE: High bone density due to a mutation in
LDL -

receptor - ***related***
protein
5

COMMENT: Comment in: N Engl J Med. 2002
May 16;346(20):1572-4.

PubMed ID: 12015398
Comment in: N Engl J Med. 2002 Sep
19;347(12):943-4; author
reply 943-4. PubMed ID: 12239268
Comment in: N Engl J Med. 2002 Sep
19;347(12):943-4; author
reply 943-4. PubMed ID: 12240686
Comment in: N Engl J Med. 2004 May
13;350(20):2096-9;
author reply 2096-9. PubMed ID:

15141052
AUTHOR: Boyden Lynn M; Mao Junhao; Belsky
Joseph; Mitzner Lyle;
Farhi Anita; Mitnick Mary A; Wu Dianqing;
Insogna Karl;

Lifton Richard P
CORPORATE SOURCE: Department of Genetics,
Yale University School of Medicine,
New Haven, Connecticut 06510, USA.

CONTRACT NUMBER: AG15345 (NIA)
AR46032 (NIAMS)
CA85420 (NCI)
RR00125 (NCRR)

SOURCE: New England journal of medicine,
(2002 May 16) 346 (20)
1513-21.

Journal code: 0255562. ISSN: 1533-4406.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020517

Last Updated on STN: 20020926
Entered Medline: 20020522

AB BACKGROUND: Osteoporosis is a major public health problem of largely unknown cause. Loss-of-function mutations in the gene for low-density lipoprotein receptor-related protein 5 (***LRP5***), which acts in the Wnt signaling pathway, have been shown to cause osteoporosis-pseudoglioma.

METHODS: We performed genetic and biochemical analyses of a kindred with

an autosomal dominant syndrome characterized by high bone density, a wide and deep mandible, and torus palatinus. RESULTS: Genetic analysis revealed linkage of the syndrome to chromosome 11q12-13 (odds of linkage, >1 million to 1), an interval that contains ***LRP5***. Affected members of the kindred had a mutation in this gene, with valine substituted for glycine at codon 171 (LRP5V171). This mutation segregated with the trait in the family and was absent in control subjects. The normal glycine lies in a so-called propeller motif that is highly conserved from fruit flies to humans. Markers of bone resorption were normal in the affected subjects, whereas markers of bone formation such as osteocalcin were markedly elevated. Levels of fibronectin, a known target of signaling by Wnt, a developmental protein, were also elevated. In vitro studies showed that the normal inhibition of Wnt signaling by another protein, Dickkopf-1 (Dkk-1), was defective in the presence of LRP5V171 and that this resulted in increased signaling due to unopposed Wnt activity. CONCLUSIONS: The LRP5V171 mutation causes high bone density, with a thickened mandible and torus palatinus, by impairing the action of a normal antagonist of the Wnt pathway and thus increasing Wnt signaling. These findings demonstrate the role of altered ***LRP5*** function in high bone mass and point to Dkk as a potential target for the prevention or treatment of osteoporosis.

L7 ANSWER 62 OF 68 MEDLINE on STN
 DUPLICATE 26
 ACCESSION NUMBER: 2002308401 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12050670
 TITLE: Kremen proteins are Dickkopf receptors that regulate Wnt/beta-catenin signalling.
 AUTHOR: Mao Bingyu; Wu Wei; Davidson Gary; Marhold Joachim; Li Mingfa; Mechler Bernard M; Delius Hajo; Hoppe Dana; Stannek Peter; Walter Carmen; Glinka Andrei; Niehrs Christof
 CORPORATE SOURCE: Molecular Embryology Division, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany.
 SOURCE: Nature, (2002 Jun 6) 417 (6889) 664-7.
 Journal code: 0410462. ISSN: 0028-0836.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AJ457192
 ENTRY MONTH: 200207

ENTRY DATE: Entered STN: 20020611
 Last Updated on STN: 20020703
 Entered Medline: 20020702
 AB The Wnt family of secreted glycoproteins mediate cell cell interactions during cell growth and differentiation in both embryos and adults. Canonical Wnt signalling by way of the beta-catenin pathway is transduced by two receptor families. Frizzled proteins and lipoprotein-receptor-related proteins 5 and 6 (***LRP5*** /6) bind Wnts and transmit their signal by stabilizing intracellular beta-catenin. Wnt/beta-catenin signalling is inhibited by the secreted protein Dickkopf1 (Dkk1), a member of a multigene family, which induces head formation in amphibian embryos. Dkk1 has been shown to inhibit Wnt signalling by binding to and antagonizing ***LRP5*** /6. Here we show that the transmembrane proteins Kremen1 and Kremen2 are high-affinity Dkk1 receptors that functionally cooperate with Dkk1 to block Wnt/beta-catenin signalling. Kremen2 forms a ternary complex with Dkk1 and LRP6, and induces rapid endocytosis and removal of the Wnt receptor LRP6 from the plasma membrane. The results indicate that Kremen1 and Kremen2 are components of a membrane complex modulating canonical Wnt signalling through LRP6 in vertebrates.

L7 ANSWER 63 OF 68 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 ACCESSION NUMBER: 2002346039 EMBASE
 TITLE: The gene for high bone mass.
 AUTHOR: Johnson M.L.; Picconi J.L.; Recker R.R.
 CORPORATE SOURCE: Dr. M.L. Johnson, Osteoporosis Research Center, Creighton Univ. School of Medicine, 601 North 30th Street, Omaha, NE 68131, United States.
 MARKL@creighton.edu
 SOURCE: Endocrinologist, (2002) 12/5 (445-453).
 Refs: 79
 ISSN: 1051-2144 CODEN: EDOCEB
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 022 Human Genetics
 033 Orthopedic Surgery
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB The mass, density, and architecture of the skeleton are adapted to enable it to perform its mechanical, protective, and metabolic functions. Osteoporosis is a condition of lost adaptation characterized by decreased skeletal mass and density and increased skeletal fragility. Many diseases result in increased bone density, including osteopetrosis and Paget's

disease, but deformities or bony lesions with decreased skeletal integrity usually accompany these conditions. We have identified a kindred with high bone mass (HBM) yet normally shaped bones. Linkage analysis localized the gene for the HBM trait to chromosome 11 (11q12-13). Subsequent physical mapping and mutation analysis have identified the cause as a point mutation in the ***LDL*** ***receptor*** - ***related*** ***protein*** ***5*** (***Lrp5***) gene that results in a valine substitution for glycine at position 171 in the protein. This protein is important in the Wnt signaling pathway. The authors have hypothesized that the ***Lrp5*** gene/pathway is part of the mechanism by which bone senses mechanical load. Increased bone strength, HBM, and a phenotype resembling our human kindred develop in transgenic mice carrying the human ***Lrp5*** gene with the HBM mutation. Recent data indicate that the HBM mutation reduces the threshold for response of the skeleton to mechanical load resulting in an overadaptation to normal mechanical loads. This discovery has opened the door to understanding one of the most important paradigms in bone biology, how bones respond and adapt to mechanical loading. Understanding the mechanosensation pathway and its regulation will lead us to new treatments for osteoporosis.

L7 ANSWER 64 OF 68 MEDLINE on STN
 DUPLICATE 27
 ACCESSION NUMBER: 2002448371 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12204281
 TITLE: Cloning and expression of Xenopus ***Lrp5*** and Lrp6 genes.
 AUTHOR: Houston Douglas W; Wylie Chris
 CORPORATE SOURCE: Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA.
 CONTRACT NUMBER: F32 HD40716-01 (NICHD)
 SOURCE: Mechanisms of development, (2002 Sep) 117 (1-2) 337-42.
 Journal code: 9101218. ISSN: 0925-4773.
 PUB. COUNTRY: Ireland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AF276084; GENBANK-BG017115
 ENTRY MONTH: 200304
 ENTRY DATE: Entered STN: 20020904
 Last Updated on STN: 20030410
 Entered Medline: 20030409
 AB ***LRP5*** and LRP6 comprise a subfamily of lipoprotein-receptor related proteins that function as co-receptors for ***Wnt***

proteins. Mutation of human ***LRP5*** is responsible for osteoporosis-pseudoglioma syndrome and disruption of Lrp6 in mice causes similar effects to mutation of several different Wnt genes. We have cloned Xenopus homologues of ***Lrp5*** and Lrp6 (Xlrp5, Xlrp6) and examined their expression during embryogenesis. Both genes are expressed maternally and ubiquitously through early development. At later stages, Xlrp5 is found in the eye, forebrain, hindbrain, branchial arches and the tip of the tail bud. Xlrp6 is expressed throughout the central nervous system, branchial arches, in the eye and otic vesicle. Both genes are also expressed at the intersomitic boundary. These results suggest roles for Wnt signaling via LRP proteins in these tissues.
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L7 ANSWER 65 OF 68 MEDLINE on STN
 DUPLICATE 28
 ACCESSION NUMBER: 2002219603 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11956231
 TITLE: Cbfa1-independent decrease in osteoblast proliferation, osteopenia, and persistent embryonic eye vascularization in mice deficient in ***Lrp5***, a Wnt coreceptor.
 AUTHOR: Kato Masaki; Patel Millan S; Levasseur Regis; Lobov Ivan; Chang Benny H-J; Glass Donald A 2nd; Hartmann Christine; Li Lan; Hwang Tae-Ho; Brayton Cory F; Lang Richard A; Karsenty Gerard; Chan Lawrence
 CORPORATE SOURCE: Department of Molecular and Cellular Biology and Medicine, Baylor College of Medicine, Houston, TX 77030, USA.
 CONTRACT NUMBER: AR42919 (NIAMS)
 DE11290 (NIDCR)
 DK58882 (NIDDK)
 HL16512 (NHLBI)
 HL51586 (NHLBI)
 SOURCE: Journal of cell biology, (2002 Apr 15) 157 (2) 303-14.
 Journal code: 0375356. ISSN: 0021-9525.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; Space Life Sciences
 ENTRY MONTH: 200205
 ENTRY DATE: Entered STN: 20020417
 Last Updated on STN: 20030105
 Entered Medline: 20020516
 AB The low-density lipoprotein receptor-related protein (Lrp)-5 functions as a Wnt coreceptor. Here we show that mice with a targeted disruption of ***Lrp5*** develop a low bone mass phenotype. In vivo and in vitro analyses indicate that this phenotype becomes evident postnatally, and

demonstrate that it is secondary to decreased osteoblast proliferation and function in a Cbfa1-independent manner. ***Lrp5*** is expressed in osteoblasts and is required for optimal Wnt signaling in osteoblasts. In addition, ***Lrp5***-deficient mice display persistent embryonic eye vascularization due to a failure of macrophage-induced endothelial cell apoptosis. These results implicate ***Wnt*** proteins in the postnatal control of vascular regression and bone formation, two functions affected in many diseases. Moreover, these features recapitulate human osteoporosis-pseudoglioma syndrome, caused by ***LRP5*** inactivation.

L7 ANSWER 66 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2001471554 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11516963
 TITLE: Wnt signalling: antagonistic Dickkopfs.
 COMMENT: Comment on: Curr Biol. 2000 Dec 14-28;10(24):1611-4. PubMed ID: 11137016
 Comment on: Curr Biol. 2001 Jun 26;11(12):951-61. PubMed ID: 11448771
 AUTHOR: Zorn A M
 CORPORATE SOURCE: Wellcome/CRC Institute of Cancer and Developmental Biology, Tennis Court Road, Cambridge CB2 1QR, UK.

SOURCE: Current biology : CB, (2001 Aug 7) 11 (15) R592-5.
 Journal code: 9107782. ISSN: 0960-9822.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Commentary
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 20010823
 Last Updated on STN: 20020424
 Entered Medline: 20011204

AB Dickkopf proteins are secreted antagonists of the Wnt cell signalling molecules, which have a novel mode of action. Dickkopf1 binds to the ***LRP5*** /6 Wnt co-receptor and prevents the formation of active Wnt-Frizzled- ***LRP5*** /6 receptor complexes, thus blocking the canonical Wnt-beta-catenin pathway.

L7 ANSWER 67 OF 68 MEDLINE on STN
 DUPLICATE 29
 ACCESSION NUMBER: 2001673198 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11719191
 TITLE: ***LDL*** ***receptor*** - ***related***
 protein ***5*** (***LRP5***) affects bone accrual and eye development.
 AUTHOR: Gong Y; Slee R B; Fukai N; Rawadi G; Roman-Roman S; Reginato A M; Wang H; Cundy T; Glorieux F H; Lev D;

Zacharin M; Oexle K; Marcelino J; Suwairi W; Heeger S;
 Sabatakos G; Apte S; Adkins W N;
 Allgrove J;
 Arslan-Kirchner M; Batch J A; Beighton P;
 Black G C; Boles R G; Boon L M; Borrone C; Brunner H G;
 Carle G F;
 Dallapiccola B; De Paepe A; Floege B;
 Halfhide M L; Hall B;
 Hennekam R C; Hirose T; Jans A; Juppner H; Kim C A;
 Keppler-Noreuil K; Kohlschuetter A;
 LaCombe D; Lambert M;
 Lemyre E; Letteboer T; Peltonen L;
 Ramesar R S; Romanengo M; Somer H; Steichen-Gersdorf E;
 Steinmann B; Sullivan B;
 Superti-Furga A; Swoboda W; van den Boogaard M J; Van Hul W; Vikkula M; Votruba M; Zabel B; Garcia T; Baron R; Olsen B R; Warman M L

CORPORATE SOURCE: Osteoporosis-Pseudoglioma Syndrome Collaborative Group.
 SOURCE: Cell, (2001 Nov 16) 107 (4) 513-23.
 Journal code: 0413066. ISSN: 0092-8674.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200201
 ENTRY DATE: Entered STN: 20011126
 Last Updated on STN: 20030403
 Entered Medline: 20020108

AB In humans, low peak bone mass is a significant risk factor for osteoporosis. We report that ***LRP5***, encoding the low-density lipoprotein receptor-related protein 5, affects bone mass accrual during growth. Mutations in ***LRP5*** cause the autosomal recessive disorder osteoporosis-pseudoglioma syndrome (OPPG). We find that OPPG carriers have reduced bone mass when compared to age- and gender-matched controls. We demonstrate ***LRP5*** expression by osteoblasts in situ and show that ***LRP5*** can transduce Wnt signaling in vitro via the canonical pathway. We further show that a mutant-secreted form of ***LRP5*** can reduce bone thickness in mouse calvarial explant cultures. These data indicate that Wnt-mediated signaling via ***LRP5*** affects bone accrual during growth and is important for the establishment of peak bone mass.

L7 ANSWER 68 OF 68 MEDLINE on STN
 ACCESSION NUMBER: 2000477637 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11029007
 TITLE: LDL-receptor-related proteins in Wnt signal transduction.
 AUTHOR: Tamai K; Semenov M; Kato Y; Spokony R; Liu C; Katsuyama Y; Hess F; Saint-Jeannet J P; He X

CORPORATE SOURCE: Division of Neuroscience,
Children's Hospital, Harvard
Medical School, Boston, Massachusetts
02115, USA.
SOURCE: Nature, (2000 Sep 28) 407 (6803)
530-5.

Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF276084
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20021228
Entered Medline: 20001030

AB The Wnt family of secreted signalling molecules are essential in embryo development and tumour formation. The Frizzled (Fz) family of serpentine receptors function as Wnt receptors, but how Fz proteins transduce signalling is not understood. In Drosophila, arrow phenocopies the wingless (DWnt-1) phenotype, and encodes a transmembrane protein that is homologous to two members of the mammalian low-density lipoprotein receptor (LDLR)-related protein (LRP) family, ***LRP5*** and LRP6 (refs 12-15). Here we report that LRP6 functions as a co-receptor for Wnt signal transduction. In Xenopus embryos, LRP6 activated Wnt-Fz signalling, and induced Wnt responsive genes, dorsal axis duplication and neural crest formation. An LRP6 mutant lacking the carboxyl intracellular domain blocked signalling by Wnt or Wnt-Fz, but not by Dishevelled or beta-catenin, and inhibited neural crest development. The extracellular domain of LRP6 bound Wnt-1 and associated with Fz in a Wnt-dependent manner. Our results indicate that LRP6 may be a component of the Wnt receptor complex.

=> log y